Access DB# 78017

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: C. DELACROIX Examiner #: 71100 Date: 10/9/02
Art Unit: 1614 Phone Number 306-3227 Serial Number: 09/726,308
Mail Box and Bldg/Room Location: 2D04 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need. #2

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): PLEASE SEE ATTACHED

Earliest Priority Filing Date: _____

Point of Contact:
~~Beverly Shears~~
Technical Info. Specialist
CM1 1E05 Tel: 308-4994

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search a composition for lowering serum cholesterol levels or preventing elevated blood serum cholesterol levels, the composition comprising:

(a) a phytosterol, → sitosterol

(b) a compound that inhibits squalene synthase and/or HMG-CoA reductase, wherein the compound is derived from the plant Polygonum multiflorum

and

(c) a compound that inhibits Acyl-CoA acyl transferase and/or a compound that activates cholesterol 7α-hydroxylase, isolated from Chrysanthemum morifolorum

Thanks

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OCT 17 2002
TECH CENTER 1600/2900

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STAFF USE ONLY

Searcher: Beverly c4994
Searcher Phone #: _____
Searcher Location: _____
Date Searcher Picked Up: _____
Date Completed: 10-25-02
Searcher Prep & Review Time: 12
Clerical Prep Time: _____
Online Time: 27

Type of Search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) _____
Bibliographic _____
Litigation _____
Fulltext _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN ✓
Dialog _____
Questel/Orbit _____
Dr.Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify) _____

PTO-1590 (8-01)

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     FILE 'REGISTRY' ENTERED AT 12:30:45 ON 25 OCT 2002
                E PHYTOSTEROL/CN 5
                E SITOSTEROL/CN 5
L1            1 S E3

                E SQUALENE SYNTHASE/CN 5
L4           15 S SQUALENE SYNTHASE ?/CN
                E "HMG-COA REDUCTASE"/CN 5
L5           13 S "HMG-COA REDUCTASE"?/CN

                E "ACYL-COA ACYLTRANSFERASE"/CN 5
L7            1 S E3
                E "7-.ALPHA.-HYDROXYLASE"/CN 5
                E ".ALPHA.-HYDROXYLASE"/CN 5

L12          16 S SQUALENE SYNTHASE?/CN


                E CHOLESTEROL/CN 5
L17           1 S E3

     FILE 'HCAPLUS' ENTERED AT 12:43:39 ON 25 OCT 2002
L1            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  SITOSTEROL/CN
L2        13503 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 OR PHYTOSTEROL OR
                SITOSTEROL OR (PHYTO OR SITO)(W)STEROL
L5           13 SEA FILE=REGISTRY ABB=ON  PLU=ON  "HMG-COA REDUCTASE"?/CN

L7            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "ACYL-COA ACYLTRANSFERA
                SE"/CN
L12          16 SEA FILE=REGISTRY ABB=ON  PLU=ON  SQUALENE SYNTHASE?/CN
L17           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  CHOLESTEROL/CN
L18        3616 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2 AND (L17 OR CHOLESTER
                OL?)
L19          59 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L18 AND (L5 OR L12 OR
                SQUALENE SYNTHASE OR (HMG OR HYDROXYMETHYLGLUTARYL OR
                HYDROXY(W)(METHYLGLUTARYL OR (ME OR METHYL)(W)GLUTARYL)
                OR HYDROXYMETHYL GLUTARYL)(W)((CO ENZYME OR COENZYME)(W)A
                 OR COA) OR HMGCOA OR (POLYG? OR P)(W)MULTIFLOR?)
L20          16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L19 AND (L7 OR ACYL(W)(C
                OA OR (COENZYME OR CO ENZYME)(W)A) OR HYDROXYLASE OR
                (CHRYSANT? OR C)(W)MORIFLOR?)

L20  ANSWER 1 OF 16  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:429411  HCAPLUS
DOCUMENT NUMBER:          137:24317
TITLE:                    Cholesterol lowering supplement
                          containing phytosterols
INVENTOR(S):              Qi, Chen; De Bont, Hendricus Bartholomeus
                          Andreas; Van der Zee, Luutsche; Lansink, Mirian;
                          Van Norren, Klaske
PATENT ASSIGNEE(S):       Neth.
SOURCE:                   U.S. Pat. Appl. Publ., 7 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:
```

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002068095	A1	20020606	US 2000-726308	20001201
WO 2002043506	A2	20020606	WO 2001-NL866	20011129

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-726308 A 20001201

AB The invention provides a compn. and a ~~method~~ for lowering blood serum **cholesterol** levels or for preventing elevated blood serum **cholesterol** levels, as well as suitable compn. comprising (a) one or more **phytosterols** and/or phytostanols or a mixt. thereof capable of reducing **cholesterol** absorption in the intestine, (b) a compn. capable of inhibiting **cholesterol** biosynthesis, and (c) a compn. capable of increasing **cholesterol** metab., wherein at least one of compns. b. and c. is preferably derived from plants. A capsule contained **phytosterol** mist. including brapiscasterol, campesterol, stigmasterol, and **sitosterol**, Radix **Polygoni multiflora** est., and Flos Chrysanthemi ext.

IT **57-88-5, Cholesterol,** biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**cholesterol** lowering supplement contg. **phytosterols**)

IT **9028-35-7, HMG-CoA** reductase
9054-54-0, Acyl-CoA acyltransferase
9077-14-9, Squalene synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; **cholesterol** lowering supplement contg. **phytosterols**)

L20 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:32338 HCAPLUS
DOCUMENT NUMBER: 136:216137
TITLE: Hawthorn fruit is hypolipidemic in rabbits fed a high **cholesterol** diet
AUTHOR(S): Zhang, Zesheng; Ho, Walter K. K.; Huang, Yu; James, Anthony E.; Lam, Lik Wang; Chen, Zhen-Yu
CORPORATE SOURCE: Department of Biochemistry, Chinese University of Hong Kong, Hong Kong, Peop. Rep. China
SOURCE: Journal of Nutrition (2002), 132(1), 5-10
CODEN: JONUAI; ISSN: 0022-3166
PUBLISHER: American Society for Nutritional Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB New Zealand white male rabbits were fed diet with no **cholesterol** added (NC), high-**cholesterol** diet (HC, 1 g/100 g feed), and HC diet with 2 g hawthorn fruit powder/100 g feed (HC-H) for 12 wk. Blood serum total **cholesterol** (TC)

and triacylglycerol (TG) levels were decreased 23.4 and 22.2%, resp., in the HC-H vs. HC group. Hawthorn feeding led to 50.6% decrease in **cholesterol** accumulation in the aorta and 23-95% greater excretion of neutral and acidic sterols. Hawthorn feeding did not affect the activities of hepatic 3-hydroxy-3-methylglutaryl CoA reductase or **cholesterol** 7.alpha.-**hydroxylase** (CH), but it decreased the activity of intestinal **acyl CoA:cholesterol** acyltransferase (ACAT). The mechanism by which dietary hawthorn fruit may decrease blood serum **cholesterol** levels may involve inhibition of **cholesterol** absorption mediated by down-regulation of intestinal ACAT enzyme activity.

IT **57-88-5D, Cholesterol,** esters **9028-35-7,** 3-Hydroxy-3-methylglutaryl CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(dietary hawthorn fruit is hypolipidemic in **cholesterol** -fed rabbits)

IT **57-88-5, Cholesterol,** biological studies
RL: BSU (Biological study, unclassified); FFD (Food or feed use); BIOL (Biological study); USES (Uses)
(dietary hawthorn fruit is hypolipidemic in **cholesterol** -fed rabbits)

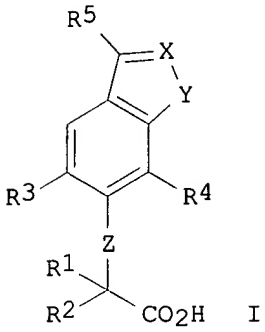
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:617987 HCAPLUS
DOCUMENT NUMBER: 135:180757
TITLE: Preparation of 1,2-benzoxazolyloxyacetic acids and analogs as PPAR agonists for treatment of diabetes and lipid disorders
INVENTOR(S): Liu, Kun; Xu, Libo; Jones, A. Brian
PATENT ASSIGNEE(S): Merck + Co. Inc., USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

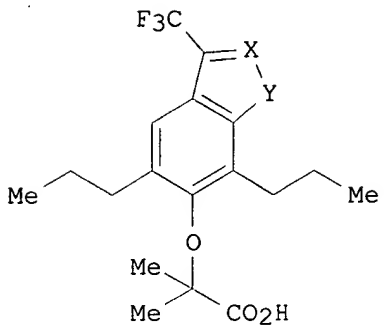
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001060807	A1	20010823	WO 2001-US4636	20010214

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-183593P P 20000218
OTHER SOURCE(S): MARPAT 135:180757
GI



I



II

AB The title compds. (I) [wherein R1 and R2 = independently H, F, (halo)alkyl, (halo)alkenyl, (halo)alkynyl; or R1 and R2 may form a cycloalkyl group; R3 and R4 = independently (fluoro)alkyl, (fluoro)alkenyl, (fluoro)alkynyl, or Cl; X = N or CR; Y = O, S, nor NR; Z = O or S; R = independently H or optionally fluoro- or alkoxy-substituted (cyclo)alkyl(oxy), alkenyl(oxy), or alkynyl(oxy); R5 = H or (un)substituted alkyl, alkenyl, alkynyl, (hetero)aryl(oxy), heterocyclyl(oxy), etc.; and pharmaceutically acceptable salts and prodrugs thereof] were prepd. For example, 2,4-dihydroxy-3,5-dipropyl-1',1',1'-trifluoroacetophenone oxime was acetylated and then treated with pyridine and TEA to give 5,7-dipropyl-6-hydroxy-3-trifluoromethyl-1,2-benzisoxazole. Etherification with Me .alpha.-bromoisobutyrate in the presence of Cs2CO3 in DMF, followed by sapon., afforded the 1,2-benzoxazolyloxyacetic acid (II). I are potent agonists of peroxisome proliferator activated receptor (PPAR) .alpha. and/or .gamma. and are useful in the treatment, control, or prevention of non-insulin dependent diabetes mellitus (NIDDM), hyperglycemia, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, obesity, vascular restenosis, inflammation, and other PPAR.alpha. and/or .gamma. mediated diseases, disorders, and conditions (no data).

IT **9028-35-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministration with inhibitors of; prepn. of benzisoxazolyloxyacetic acid PPAR agonists via cyclization of dihydroxyacetophenone oximes for treatment of diabetes and lipid disorders)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:431184 HCAPLUS
DOCUMENT NUMBER: 135:236225
TITLE: Hepatic **cholesterol** and bile acid synthesis, low-density lipoprotein receptor function, and plasma and fecal sterol levels in mice: effects of apolipoprotein E deficiency and

probucol or **phytosterol** treatment

AUTHOR(S): Moghadasian, Mohammed H.; Nguyen, Lien B.; Shefer, Sarah; Salen, Gerald; Batta, Ashok K.; Frohlich, Jiri J.

CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, St. Paul's Hospital and University of British Columbia, Vancouver, BC, V6Z 1Y6, Can.

SOURCE: Metabolism, Clinical and Experimental (2001), 50(6), 708-714
CODEN: METAAJ; ISSN: 0026-0495

PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We compared hepatic **cholesterol** metab. in apolipoprotein (apo) E-knockout (KO) mice with their wild-type counterparts. We also investigated the effects of treatment with **phytosterols** or probucol on the activity of hepatic 3-hydroxy-3-methyl-glutaryl CoA (**HMG-CoA**) reductase (**cholesterol** synthesis), **cholesterol** 7.alpha.-**hydroxylase** and sterol 27-**hydroxylase** (bile acid synthesis), and low-d. lipoprotein (LDL) receptor function in this animal model of atherogenesis. These findings were then related to treatment-induced changes in plasma, hepatic, and fecal sterol concns. Mouse liver membranes have binding sites similar to LDL receptors; the receptor-mediated binding represents 80% of total binding and is LDL concn.-dependent. These binding sites have higher affinity for apo E-contg. particles than apo B only-contg. particles. Deletion of apo E gene was assocd. with several-fold increases in plasma **cholesterol** levels, 1.5-fold increase in hepatic **cholesterol** concns., 50% decrease in **HMG-CoA** reductase activity, 30% increase in **cholesterol** 7.alpha.-**hydroxylase** and 25% decrease in LDL receptor function. Treatment of apo E-KO mice with either probucol or **phytosterols** significantly reduced plasma **cholesterol** levels. **Phytosterols** significantly increased the activity of hepatic **HMG-CoA** reductase, and probucol significantly increased **cholesterol** 7.alpha.-**hydroxylase** activity. Neither treatment significantly altered hepatic LDL receptor function. **Phytosterols**, but not probucol, significantly increased fecal sterol excretion and decreased hepatic **cholesterol** concns. Plasma **cholesterol** lowering effects of **phytosterols** and probucol are due to different mechanisms: stimulation of **cholesterol** catabolism via increased bile acid synthesis by probucol and decreased **cholesterol** absorption by **phytosterols**. In the absence of apo E, hepatic LDL receptors could not be upregulated and did not contribute to the **cholesterol** lowering effects of either agent.

IT **57-88-5, Cholesterol**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(probucol or **phytosterol** treatment and apolipoprotein E deficiency effect on hepatic **cholesterol** and bile acids, low-d. lipoprotein receptor, and plasma and fecal sterol)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:176368 HCAPLUS
DOCUMENT NUMBER: 134:295127
TITLE: Feeding unsaponifiable compounds from rice bran oil does not alter hepatic mRNA abundance for **cholesterol** metabolism-related proteins in hypercholesterolemic rats
AUTHOR(S): Nagao, Koji; Sato, Masao; Takenaka, Miyuki; Ando, Miyuki; Iwamoto, Masako; Imaizumi, Katsumi
CORPORATE SOURCE: Laboratory of Nutrition Chemistry, Division of Bioscience and Biotechnology, Faculty of Agriculture, Graduate School Kyushu University, Fukuoka, 812-8581, Japan
SOURCE: Bioscience, Biotechnology, and Biochemistry (2001), 65(2), 371-377
CODEN: BBBIEJ; ISSN: 0916-8451
PUBLISHER: Japan Society for Bioscience, Biotechnology, and Agrochemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The hypocholesterolemic effects of rice bran oil (RBO) have been defined in human and animal expts. and indicate the presence of active component(s) in the oil unsaponifiable fraction, but the mechanism of action is not known. Exogenously hypercholesterolemic (ExHC) rats were fed for 2 wk a 0.5% **cholesterol** diet with 10% RBO, RBO-simulating oil (RBOSO) in its fatty acid compn., or RBOSO plus 0.25% unsaponifiable compds. (UC) from RBO. Rats fed RBO or UC had decreased blood serum and liver **cholesterol** concns. and no decrease in high-d. lipoprotein **cholesterol** levels. Dietary RBO and UC elevated fecal neutral sterol excretion, but no significant changes in fecal bile acid excretion or hepatic abundance of mRNA for 3-hydroxy-3-methylglutaryl-CoA reductase, **cholesterol**-7.alpha.-**hydroxylase**, and low-d. lipoprotein receptor were seen. Blood serum and liver .alpha.-tocopherol concns. were decreased in RBO or UC fed rats. Thus, the UC in RBO can decrease blood serum **cholesterol** concns. by interrupting the absorption of intestinal hydrophobic compds. rather than by modifying **cholesterol** metab. in the liver.
IT **9028-35-7**, 3-Hydroxy-3-methylglutaryl CoA reductase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(dietary rice bran oil unsaponifiable fraction does not alter abundance of hepatic mRNA for **cholesterol** metab. related proteins in hypercholesterolemic rats)
IT **57-88-5**, **Cholesterol**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); FFD (Food or feed use); BIOL (Biological study); PROC (Process); USES (Uses)
(dietary rice bran oil unsaponifiable fraction does not alter abundance of hepatic mRNA for **cholesterol** metab. related proteins in hypercholesterolemic rats)
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:729798 HCAPLUS
DOCUMENT NUMBER: 134:320705
TITLE: Effects of simvastatin on hepatic **cholesterol** metabolism, bile lithogenicity and bile acid hydrophobicity in patients with gallstones
AUTHOR(S): Smith, Jeffery L.; Roach, Paul D.; Wittenberg, Leonie N.; Riottot, Michel; Pillay, S. Praga; Nestel, Paul J.; Nathanson, Les K.
CORPORATE SOURCE: Lipid Metabolism Laboratory, Department of Surgery Royal Brisbane Hospital, The University of Queensland, Brisbane, Australia
SOURCE: Journal of Gastroenterology and Hepatology (2000), 15(8), 871-879
CODEN: JGHEEO; ISSN: 0815-9319
PUBLISHER: Blackwell Science Asia Pty Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB There is limited information available on the effects of 3-hydroxy-3-methyl-glutaryl CoA reductase inhibitors on hepatic and biliary **cholesterol** metab. in patients with gallstones. The aims of this study were to det. the effect of simvastatin on the regulatory elements of **cholesterol** metab. that det. the concns. of **cholesterol** in plasma and bile. Thirty-one gallstone patients were enrolled in the study; 17 were treated with 20 mg simvastatin daily for 3 wk prior to cholecystectomy and 14 served as controls. Samples of blood, liver, gall-bladder bile and bile from the common bile duct (CBD) were collected and analyzed. The plasma **cholesterol** (-30%), triacylglycerol (-23%) and low-d. lipoprotein (LDL) **cholesterol** (-42%) concns. were significantly lowered by simvastatin treatment, as was the plasma lathosterol: **cholesterol** (-70%), which reflects whole-body **cholesterol** synthesis. Despite these changes, the hepatic LDL receptor protein and LDL receptor activity in circulating mononuclear cells were similar in both groups. There were no differences in the plasma **phytosterol**: **cholesterol**, which reflects the intestinal **cholesterol** absorption capacity or in the activity of hepatic **acyl-CoA**: **cholesterol** acyltransferase. There were however, lower **cholesterol** concns. in CBD (-68%) and gall bladder (-41%) bile, and decreased lithogenic (-47%) and bile acid hydrophobicity (-22%) indexes of CBD bile in the simvastatin group. These data indicate that simvastatin reduced plasma and biliary **cholesterol** levels primarily by reducing **cholesterol** synthesis. The redn. in CBD bile lithogenicity and bile acid hydrophobicity by simvastatin suggests that this agent may be useful for people who have early stages of **cholesterol** gallstone development and in whom a choleretic effect is required.
IT **9028-35-7**, 3-Hydroxy-3-methyl-glutaryl CoA reductase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors, statins; effects of simvastatin on hepatic **cholesterol** metab., bile lithogenicity and bile acid hydrophobicity in patients with gallstones)
IT **57-88-5**, **Cholesterol**, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU

(Occurrence); PROC (Process)
(low-d. lipoprotein; effects of simvastatin on hepatic **cholesterol** metab., bile lithogenicity and bile acid hydrophobicity in patients with gallstones)
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:221557 HCAPLUS
DOCUMENT NUMBER: 131:44173
TITLE: Histologic, hematologic, and biochemical characteristics of apo E-deficient mice: effects of dietary **cholesterol** and **phytosterols**
AUTHOR(S): Moghadasian, Mohammed H.; Nguyen, Lien B.; Shefer, Sarah; McManus, Bruce M.; Frohlich, Jiri J.
CORPORATE SOURCE: Healthy Heart Program, Department of Pathology and Laboratory Medicine, St. Paul's Hospital and University of British Columbia, Vancouver, BC, V6Z 1Y6, Can.
SOURCE: Laboratory Investigation (1999), 79(3), 355-364
CODEN: LAINAW; ISSN: 0023-6837
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this study, we examd. the effects of a "Western-type" diet contg. 9% (wt./wt.) fat and 0.15% (wt./wt.) **cholesterol**, in the presence or absence of 2% (wt./wt.) **phytosterol** mixt. over an 18-wk period in apolipoprotein E-deficient mice. Addn. of **phytosterols** to the high **cholesterol** diet was assocd. with normalization of the depressed hepatic 3-hydroxy-3-methylglutaryl-CoA reductase activity (from 22.3 .+-. 6.3 to 55.4 .+-. 19.9 pmol/mg protein/min, $p < 0.05$). This finding was assocd. with a significant decrease in plasma and hepatic **cholesterol** concns. compared with animals fed the high **cholesterol** diet without **phytosterols** (33.3 .+-. 5.0 vs. 19.2 .+-. 6.2 pmol/mg protein, $p < 0.05$). The activities of **cholesterol** 7.alpha.-**hydroxylase** and sterol 27-**hydroxylase** were comparable between the two groups of mice. Urinalyses and hematol. data were comparable between the two groups except for significantly lower platelet counts in the **phytosterol**-treated animals (681.6 .+-. 118.9 vs. 857.1 .+-. 185.4 .times. 109/L, $p < 0.05$). The **phytosterol**-treated animals had significantly ($p < 0.05$) less fragile erythrocytes when exposed to 0.08, 0.07, or 0.05 M NaCl compared with **cholesterol**-fed mice. The consumption of the Western-type diet was assocd. with the development of xanthomatous skin lesions in 33% of the **cholesterol**-fed animals, but in none of the **phytosterol**-treated animals. Histol. examn. revealed oil red O-neg. vacuolation in liver and kidney parenchymal cells of the **cholesterol**-fed group, but not in the **phytosterol** -treated mice. Arrested spermatogenesis and atrophy of seminiferous tubules were obsd., to a variable extent, in both groups of animals. We conclude that addn. of the **phytosterol** mixt. (2% wt./wt.) to a Western-type diet in apolipoprotein E-deficient mice significantly decreases plasma and hepatic **cholesterol**

concns., increases hepatic 3-hydroxy-3-methylglutaryl-CoA reductase activity, and prevents cutaneous xanthomatosis and vacuolation in the parenchymal cells of kidneys and livers.

IT **9028-35-7**, 3-Hydroxy-3-methylglutaryl CoA reductase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(histol., hematol., and biochem. characteristics of apo E-deficient mice and effects of dietary **cholesterol** and **phytosterols**)

IT **57-88-5**, **Cholesterol**, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(histol., hematol., and biochem. characteristics of apo E-deficient mice and effects of dietary **cholesterol** and **phytosterols**)

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:324209 HCAPLUS
DOCUMENT NUMBER: 129:40550
TITLE: **Cholesterol** inhibits bile acid synthesis in New Zealand white and Watanabe heritable hyperlipidemic rabbits
AUTHOR(S): Salen, G.; Xu, G.; Shefer, S.; Ness, G. C.; Parker, T. S.
CORPORATE SOURCE: Div. Gastroenterol, New Jersey Medical Sch., Newark, NJ, 07103-2757, USA
SOURCE: Falk Symposium (1996), 84(Bile Acids, Cholestasis, Gallstones), 3-12
CODEN: FASYDI; ISSN: 0161-5580
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Plasma **cholesterol** levels were 9.9 times greater in Watanabe heritable hyperlipidemic (WHHL) than New Zealand white (NZW) rabbits fed a control diet devoid of **cholesterol**. A 0.2 **cholesterol** diet increased plasma **cholesterol** .apprx.2-fold in both rabbit groups, and the exptl. 2% **cholesterol** diet increased plasma **cholesterol** 26-fold in the NZW rabbits after 10 days. Liver **cholesterol** levels were also increased, and **HMG-CoA** reductase and **cholesterol** 7.alpha.-**hydroxylase** were decreased by increasing dietary **cholesterol** levels. The mRNAs for the 2 enzymes were decreased by the 2% **cholesterol** diet only in NZW rabbits, but tended to be higher in these rabbits than in WHHL rabbits, leading to reduced **cholesterol** metab. and bile acid synthesis in the latter rabbits. Effects of 0.2% dietary **sitosterol** are also discussed.

IT **57-88-5**, **Cholesterol**, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**cholesterol** inhibits bile acid synthesis in New

Zealand white and Watanabe heritable hyperlipidemic rabbits)

IT **9028-35-7**, **HMG-CoA** reductase
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(**cholesterol** inhibits bile acid synthesis in New Zealand white and Watanabe heritable hyperlipidemic rabbits)

L20 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:312075 HCAPLUS
DOCUMENT NUMBER: 129:80023
TITLE: Sitosterolemia: exclusion of genes involved in reduced **cholesterol** biosynthesis
AUTHOR(S): Patel, Shailendra B.; Honda, Akira; Salen, Gerald
CORPORATE SOURCE: Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, TX, 75235-9052, USA
SOURCE: Journal of Lipid Research (1998), 39(5), 1055-1061
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: Lipid Research, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sitosterolemia (phytosterolemia) is a rare autosomal recessively inherited disorder that is characterized by premature coronary artery disease, xanthomas, and increased plasma plant sterols and 5.alpha.-stanols. Affected individuals show an increased absorption of both **cholesterol** and **sitosterol** from the diet, decreased bile clearance of these sterols and their metabolites resulting in markedly expanded whole body **cholesterol** and **sitosterol** pools. Biochem. studies have shown that the regulation of the **cholesterol** biosynthetic pathway may be abnormal in this condition. In particular, the activities and mRNA for the biosynthetic enzymes, 3-hydroxy-3-methylglutaryl CoA (**HMG-CoA**) reductase and **HMG-CoA** synthase are low in liver biopsy specimens isolated from affected individuals, suggesting replete intracellular **cholesterol** pools. However, the membrane expression of hepatocyte low d. lipoprotein receptors was increased, suggesting discordant regulation. Segregation analyses in three families for the genes for **HMG-CoA** reductase, **HMG-CoA** synthase, and LDL-receptor excluded these as sites of mutation. In view of the previously described discordant regulation of the above genes in sitosterolemia, the two major regulatory genes for this pathway, sterol regulatory element binding proteins (SREBP-1 and -2), were also examd. These genes did not segregate with the disease and were thus excluded. Two other genes involved in **cholesterol** absorption and chylomicron secretion, namely **acyl CoA:cholesterol** acyltransferase (ACAT) and microsomal triglyceride transfer protein (MTP) were also examd. for segregation and similarly excluded. Two other genes involved in **cholesterol** absorption and chylomicron secretion, namely **acyl CoA:cholesterol** acyltransferase (ACAT) and microsomal triglyceride transfer protein (MTP) were also examd. for segregation and similarly excluded. Although the gene defect in sitosterolemia therefore remains to be elucidated,

important candidate genes have been excluded.
IT **9028-35-7, HMG-CoA** reductase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(exclusion of genes involved in reduced **cholesterol** biosynthesis and sitosterolemia)
IT **57-88-5, Cholesterol**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(exclusion of genes involved in reduced **cholesterol** biosynthesis and sitosterolemia)

L20 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:554841 HCAPLUS
DOCUMENT NUMBER: 121:154841
TITLE: The effect of increased hepatic **sitosterol** on the regulation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase and **cholesterol** 7.alpha.-**hydroxylase** in the rat and sitosterolemic homozygotes
AUTHOR(S): Shefer, Sarah; Salen, Gerald; Bullock, John; Nguyen, Lien B.; Ness, Gene C.; Vhao, Zhihong; Belamarich, Peter F.; Chowdhary, Indu; Lerner, Susan; et al.
CORPORATE SOURCE: New Jersey Medical School, Univ. of Medicine and Dentistry of New Jersey, Newark, NJ, 07103, USA
SOURCE: Hepatology (Philadelphia, PA, United States) (1994), 20(1, Pt. 1), 213-19
CODEN: HPTLD9; ISSN: 0270-9139
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors investigated hepatic **cholesterol** homeostasis in four homozygous sitosterolemic subjects from two unrelated families who showed enhanced absorption, diminished removal and increased tissue and plasma concns. of **sitosterol** (24-Et **cholesterol**). Measurements of hepatic 3-hydroxy-3-methylglutaryl CoA reductase activities were correlated with steady state mRNA levels and related to **cholesterol** 7.alpha.-**hydroxylase** activities in the sitosterolemic homozygotes and nine controls. Similar detns. were made in rats infused i.v. with **sitosterol** so that hepatic and plasma **sitosterol** concns. increased to about 10% of total sterols to resemble the human disease sitosterolemia. In the four sitosterolemic homozygotes, hepatic 3-hydroxy-3-methylglutaryl CoA reductase activities were markedly reduced (12% of normal), and steady state 3-hydroxy-3-methylglutaryl CoA reductase mRNA levels barely detected. In contrast, hepatic 3-hydroxy-3-methylglutaryl CoA reductase activities and mRNA levels were not decreased in rats with similarly elevated hepatic **sitosterol** concns. However, hepatic **cholesterol** 7.alpha.-**hydroxylase** activity was inhibited 30% in both the sitosterolemic homozygotes and rats with high liver **sitosterol** concns. Plasma **cholesterol** concns. increased 120% in the sitosterolinfused rats and 29% in the untreated human homozygotes. These results demonstrate that high-tissue **sitosterol** concns. do not inhibit hepatic 3-hydroxy-3-methylglutaryl CoA reductase activity or steady state mRNA levels and that they competitively block **cholesterol** 7.alpha.-**hydroxylase** activity and

raise plasma **cholesterol** levels. Thus the deficiency of 3-hydroxy-3-methylglutaryl CoA reductase in the liver of sitosterolemic homozygotes is inherited and not due to the hepatic accumulation of **sitosterol**. In distinction, elevated hepatic **sitosterol** concns. increase plasma **cholesterol** levels by competitively suppressing **cholesterol** 7.alpha.-**hydroxylase** activity.

IT **57-88-5, Cholesterol**, biological studies
RL: BIOL (Biological study)
(altered hepatic metab. of, in sitosterolemic humans)

IT **9028-35-7**, 3-Hydroxy-3-methylglutaryl CoA reductase
RL: BIOL (Biological study)
(increased hepatic **sitosterol** effect on regulation of, in sitosterolemic humans)

L20 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:188362 HCAPLUS
DOCUMENT NUMBER: 118:188362
TITLE: New model to study **cholesterol** uptake in the human intestine in vitro
AUTHOR(S): Sviridov, D. D.; Safonova, I. G.; Nano, J. L.; Pavlov, M. Y.; Rampal, P.; Repin, V. S.; Smirnov, V. N.
CORPORATE SOURCE: Inst. Exp. Cardiol., Cardiol. Res. Cent., Moscow, 121552, Russia
SOURCE: Journal of Lipid Research (1993), 34(2), 331-9
CODEN: JLPRAW; ISSN: 0022-2275
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new model to study **cholesterol** uptake in the human intestine in vitro is described. Human small intestine organ cultures were incubated with mixed micelles contg. bile acid, phospholipid, and **cholesterol** or its nonabsorbable analog, **sitosterol**; trace amts. of labeled **cholesterol** or **sitosterol** were added to the micelles. After incubation, the lipids were extd. from the cells and **cholesterol** and **sitosterol** uptake were evaluated. Specific **cholesterol** uptake was detd. as a difference between **cholesterol** and **sitosterol** uptake. **Cholesterol**, but not **sitosterol**, uptake was time- and dose-dependent. Rapid and slow phases of **cholesterol** uptake were obsd. **Cholesterol** uptake was also temp.-dependent. Removal of epithelial cells from human intestine explants reduced **cholesterol**, but not **sitosterol**, uptake. Inhibition of **acyl CoA: cholesterol** acyltransferase by Sandoz compd. 58-035 and treatment with monensin reduced **cholesterol** uptake, but not **sitosterol** uptake, in a dose-dependent manner. In contrast, treatment of cultures with an inhibitor of 3-hydroxy-3-methylglutaryl CoA reductase, lovastatin, stimulated **cholesterol**, but not **sitosterol**, uptake in a dose-dependent manner; mevalonic acid reversed the effect of lovastatin. The presented model allows large-scale in vitro studies of different stages of **cholesterol** absorption in the human intestine.

IT **9028-35-7**, 3-Hydroxy-3-methyl-glutaryl coenzyme A reductase
RL: BIOL (Biological study)
(inhibition of, **cholesterol** uptake by human intestine

stimulation by)
IT **57-88-5, Cholesterol**, biological studies
RL: BIOL (Biological study)
(uptake of, by human small intestine, model for)

L20 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:116527 HCAPLUS
DOCUMENT NUMBER: 118:116527
TITLE: Effects of pravastatin on **cholesterol** metabolism in Watanabe heritable hyperlipidemic rabbits
AUTHOR(S): Amorosa, Louis F.; Rozovski, S. Jamie; Ananthakrishnan, Radha; Coly, Erasme; AlHinai, Ali; Martucci, Charles; Schneider, Stephen H.; Shimamura, Tetsuo; Khachadurian, Avedis K.
CORPORATE SOURCE: Robert Wood Johnson Med. Sch., UMDNJ, New Brunswick, NJ, 08903-0019, USA
SOURCE: Japanese Heart Journal (1992), 33(4), 451-63
CODEN: JHEJAR; ISSN: 0021-4868
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Pravastatin, a competitive inhibitor of **hydroxymethylglutaryl CoA** reductase (**HMG CoA** reductase) is a potent hypocholesterolemic agent in humans as well as exptl. animals, including the Watanabe heritable hyperlipidemic (WHHL) rabbit, lacking low d. lipoprotein (LDL) receptor activity. We studied the effect of pravastatin on several aspects of **cholesterol** metab. in WHHL rabbits. **Cholesterol** synthesis was measured by i.p. injection of radioacetate and detn. of its incorporation into the nonsaponifiable lipid fraction of liver, plasma, adrenal glands and gonads. A single dose of pravastatin (25 mg/kg) caused statistically significant inhibition of hepatic **cholesterol** synthesis at 2, 6, 12, and 24 h following oral administration. By 48 h, the inhibitory effect of the drug was no longer demonstrable. The pattern of radioactivity in the plasma was similar to that in the liver. The drug had no statistically significant effect on **cholesterol** synthesis in adrenal glands and gonads, suggesting a selective effect on the liver. **Cholesterol** absorption was studied after simultaneous oral administration of [3H] **cholesterol** and [14C] .beta.-**sitosterol**. Pravastatin, 50 mg/kg for 10 days had no effect on fetal excretion of the radiolabeled steroids over 4 days. At 24 h the plasma level of [14C] **cholesterol** was 1/3 that of control in pravastatin treated animals ($p < 0.05$) but did not undergo an accelerated decline over 6 days. The activity of **acyl CoA:cholesterol** acyltransferase (ACAT) in intestinal mucosa and the concn. of hepatic **cholesterol** were similar in animals treated over one year with pravastatin 50 mg/kg/day or with placebo. Our data do not allow us to make definitive conclusions about the effect of pravastatin on **cholesterol** absorption but are compatible with the hypothesis that the drug inhibits the hepatic synthesis as well as the assembly of **cholesterol** into lipoproteins.
IT **57-88-5**
RL: BIOL (Biological study)
(anticholesteremics and Hypolipemics, pravastatin, **cholesterol** metab. in liver and other organs in mechanism

of)
IT **57-88-5, Cholesterol**, biological studies
RL: BIOL (Biological study)
(pravastatin effect on metab. of, in liver and other organs, mechanism of hypocholesterolemic effect in relation to)

L20 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:153217 HCAPLUS
DOCUMENT NUMBER: 110:153217
TITLE: Effect of dietary n-3 polyunsaturated fatty acids on **cholesterol** synthesis and degradation in rats of different ages
AUTHOR(S): Choi, Yong Soon; Goto, Shoichiro; Ikeda, Ikuo; Sugano, Michihiro
CORPORATE SOURCE: Sch. Agric., Kyushu Univ., Fukuoka, 812, Japan
SOURCE: Lipids (1989), 24(1), 45-50
CODEN: LPDSAP; ISSN: 0024-4201
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Male Sprague-Dawley rats 4 wk or 8 mo of age were fed purified diets contg. 10% fat, either as a blend of safflower oil and palm olein (polyunsatd. fatty acids, PUFA, 34%), a blend of linseed oil and palm olein (PUFA, 33%) or sardine oil (PUFA, 33%) for 4 wk. In other trials, sterol contents were made equiv. by supplementing **cholesterol** to a blend of corn oil and palm olein (PUFA, 30%) or **phytosterol** to sardine oil (PUFA, 30%). Fish oil was hypolipidemic in rats of different ages, but it tended to increase liver **cholesterol** in adult animals and this was not improved by the addn. of **phytosterol**. The age-dependent increase in liver **cholesterol** was not duplicated in rats fed a vegetable fat blend supplemented with **cholesterol**. At both ages, liver 3-hydroxy-3-methylglutaryl CoA reductase activity was lower in the sardine oil than in the other groups. There were no age- or diet-related differences in the activity of liver **cholesterol** 7.alpha.-**hydroxylase**. Fecal steroid excretion was comparable in age-matched rats fed diets supplemented either with **cholesterol** or **phytosterol**. Sardine oil reduced the .DELTA.6-desaturase activity markedly as compared with linseed oil, and age-dependent redn. of the desaturase activity was obsd. in all dietary groups examd. Thus, there was a specific effect of fish oil on lipid metab.
IT **57-88-5, Cholesterol**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metab. of, dietary n-3 fatty acids effect on, age in relation to)
IT **57-88-5D**, Cholest-5-en-3-ol (3.beta.)-, esters
9028-35-7, 3-Hydroxy-3-methylglutaryl coenzyme A reductase
RL: BIOL (Biological study)
(of liver, dietary n-3 fatty acids effect on, age in relation to)

L20 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:152228 HCAPLUS
DOCUMENT NUMBER: 110:152228
TITLE: Effect of **sitosterol** on the rate-limiting enzymes in **cholesterol** synthesis and degradation

AUTHOR(S): Boberg, Kirsten Muri; Aakerlund, Jan Erik; Bjoerkhem, Ingemar
CORPORATE SOURCE: Inst. Clin. Biochem., Univ. Oslo, Oslo, Norway
SOURCE: Lipids (1989), 24(1), 9-12
CODEN: LPDSAP; ISSN: 0024-4201
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Attempts were made to develop an animal model for phytosterolemia. Infusion of Intralipid contg. 0.2% **sitosterol** in rats gave circulating levels of **sitosterol** of .apprx.2.5 mmol/L, which is similar to or higher than those present in patients with untreated phytosterolemia. The infusions gave serum levels of **cholesterol** nearly twice those obtained in rats infused with Intralipid alone or Intralipid contg. 0.2% **cholesterol**. The hepatic **HMG-CoA** reductase activity was unaffected or slightly increased by the **sitosterol** infusions. The **cholesterol** 7.alpha.-**hydroxylase** activity was slightly depressed. In the case of 7.alpha.-hydroxylation of endogenous **cholesterol**, the depression reached significance. The microsomal content of **sitosterol** in the **sitosterol**-infused rats was .apprx.30% of that of microsomal **cholesterol**. The effect of **sitosterol** on 7.alpha.-hydroxylation of **cholesterol** was investigated by incubations of acetone powder of rat liver microsomes with mixts. of **cholesterol** and **sitosterol**. **Sitosterol** mixed with **cholesterol** to a compn. similar to that found in the above microsomal fraction had a depressing effect on 7.alpha.-hydroxylation of **cholesterol**. This degree of depression was of the same magnitude as that found in the **sitosterol** infusion expts. The possibility is discussed that the hypercholesterolemia obtained in the .beta.-**sitosterol** -infused rats is due to the inhibitory effect of **sitosterol** on the **cholesterol** 7.alpha.-**hydroxylase**.

IT **57-88-5, Cholesterol**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metab. of, **sitosterol** effect on, phytosterolemia model in relation to)

IT **9028-35-7**, 3-Hydroxy-3-methylglutaryl-CoA reductase
RL: BIOL (Biological study)
(**sitosterol** effect on, phytosterolemia model in relation to)

L20 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1975:441966 HCAPLUS
DOCUMENT NUMBER: 83:41966
TITLE: Sterol balance studies in the rat. Effects of dietary **cholesterol** and .beta.-**sitosterol** on sterol balance and rate-limiting enzymes of sterol metabolism
AUTHOR(S): Raicht, Robert F.; Cohen, Bertram Ira; Shefer, Sarah; Mosbach, Erwin H.
CORPORATE SOURCE: Public Health Res. Inst., City of New York, Inc., New York, N. Y., USA
SOURCE: Biochim. Biophys. Acta (1975), 388(3), 374-84
CODEN: BBACAQ
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Sterol balance measurements using isotopic and chromatog. techniques were carried out in rats fed diets contg. .beta.-**sitosterol** (0.8%) and **cholesterol** (1.2%). The activities of the rate-limiting enzymes of **cholesterol** synthesis (.beta.-hydroxy-.beta.-methylglutaryl-CoA reductase, EC 1.1.1.34) and bile acid synthesis (**cholesterol** 7.alpha.-**hydroxylase**) were detd. in the same animals. **Cholesterol** feeding increased **cholesterol** absorption from 1.2 to 70 mg/day. The increased absorption was compensated for by inhibition of hepatic **cholesterol** synthesis, enhanced conversion of **cholesterol** to bile acids (from 13.7 to 27.3 mg/day) and a slight increase in the excretion of endogenous neutral steroids (from 7.7 to 11.2 mg/day). Despite the adaptation there was accumulation of **cholesterol** in the liver (from 2.2 to 9.2 mg/g). .beta.-**Sitosterol** feeding inhibited **cholesterol** absorption (calcd. absorption was zero). In these rats there was enhanced **cholesterol** synthesis (from 20.0 to 28.8 mg/day), but no change in rates of bile acid formation. Measurements of the activities of the rate-limiting enzymes showed fair correlation with **cholesterol**-bile acid balance. In **cholesterol** fed animals, .beta.-hydroxy-.beta.-methylglutaryl-CoA reductase was inhibited 80% and **cholesterol** 7.alpha.-**hydroxylase** was enhanced 61%. In .beta.-**sitosterol**-fed animals, the reductase was increased 2-fold and **cholesterol** 7.alpha.-**hydroxylase** was not significantly different from controls.

IT **57-88-5**, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, **sitosterol** effect on)

IT **9028-35-7**
RL: BIOL (Biological study)
(of liver, **cholesterol** and **sitosterol** effect on)

L20 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1973:533323 HCAPLUS
DOCUMENT NUMBER: 79:133323
TITLE: Regulatory effects of sterols and bile acids on hepatic 3-hydroxy-3-methylglutaryl CoA reductase and **cholesterol** 7.alpha.-**hydroxylase** in the rat
AUTHOR(S): Shefer, S.; Hauser, S.; Lapar, V.; Mosbach, E. H.
CORPORATE SOURCE: Public Health Res. Inst., City of New York, Inc., New York, N. Y., USA
SOURCE: J. Lipid Res. (1973), 14(5), 573-80
CODEN: JLPRAW
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The administration of bile acids (taurocholate [81-24-3], taurodeoxycholate [516-50-7], and taurochenodeoxycholate [516-35-8]) at 1% of the diet to rats for 1 week decreased the activity of hepatic microsomal 3-hydroxy-3-methylglutaryl CoA reductase (**HMG CoA** reductase) [**9028-35-7**]. Taurocholate and taurodeoxycholate, but not taurochenodeoxycholate, inhibited **cholesterol** 7.alpha.-**hydroxylase**

[9037-53-0]. Dietary **sitosterol** [83-46-5] increased the specific activity of **HMG CoA** reductase and **cholesterol** 7.alpha.-**hydroxylase**, and biliary **cholesterol** [**57-88-5**] concns. Compared with controls fed the stock diet, the simultaneous administration of **sitosterol** and taurochenodeoxycholate decreased **HMG CoA** reductase activity by 60%. **Sitosterol** and taurocholate given together to rats inhibited **cholesterol** 7.alpha.-**hydroxylase** activity. In all groups receiving bile acids, biliary secretion of bile acids was nearly doubled and bile acid compn. was shifted in the direction of the administered bile acid. The compn. of the bile acid pool seems to influence the hepatic concns. of the rate-controlling enzymes of bile acid synthesis.

IT **57-88-5**, biological studies
RL: BIOL (Biological study)
(of bile, **sitosterol** effect on)

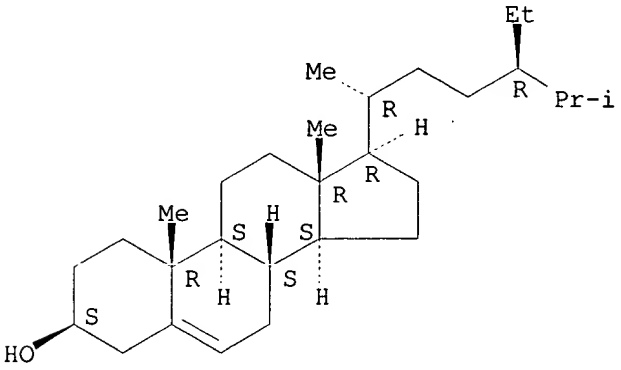
IT **9028-35-7**
RL: PROC (Process)
(of liver, bile acids and sterols regulation of)

FILE 'REGISTRY' ENTERED AT 12:48:05 ON 25 OCT 2002
L21 1 S 83-46-5/RN

L21 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN **83-46-5** REGISTRY
CN Stigmast-5-en-3-ol, (3.beta.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Nimbosterol (6CI)
CN Stigmast-5-en-3.beta.-ol (8CI)
OTHER NAMES:
CN (-)-.beta.-Sitosterol
CN (24R)-Ethylcholest-5-en-3.beta.-ol
CN (24R)-Stigmast-5-en-3.beta.-ol
CN .alpha.-Dihydrofucosterol
CN .beta.-Sitosterin
CN .beta.-Sitosterol
CN .DELTA.5-Stigmasten-3.beta.-ol
CN 22,23-Dihydrostigmasterol
CN 24.alpha.-Ethylcholesterol
CN Angelicin
CN Angelicin (steroid)
CN Azuprostat
CN Cinchol
CN Cupreol
CN Quebrachol
CN Rhamnol
CN SKF 14463
CN Sobatum
CN Stigmasterol, 22,23-dihydro-
FS STEREOSEARCH
DR 8003-23-4, 15764-35-9, 76772-70-8, 182512-23-8
MF C29 H50 O
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHEM, DDFU, DETHERM*, DIPPR*, DRUGU, EMBASE, HODOC*, IFICDB, IFIPAT, IFIUDB, IPA, MRCK*,

MSDS-OHS, NAPRALERT, NIOSHTIC, PHARMASEARCH, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, ULIDAT, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

9345 REFERENCES IN FILE CA (1962 TO DATE)
149 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
9359 REFERENCES IN FILE CAPLUS (1962 TO DATE)
12 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

FILE 'HCAPLUS' ENTERED AT 12:49:11 ON 25 OCT 2002

L1 1 SEA FILE=REGISTRY ABB=ON PLU=ON SITOSTEROL/CN
L2 13503 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR PHYTOSTEROL OR SITOSTEROL OR (PHYTO OR SITO)(W)STEROL
L5 13 SEA FILE=REGISTRY ABB=ON PLU=ON "HMG-COA REDUCTASE"?/CN
L7 1 SEA FILE=REGISTRY ABB=ON PLU=ON "ACYL-COA ACYLTRANSFERASE"/CN
L12 16 SEA FILE=REGISTRY ABB=ON PLU=ON SQUALENE SYNTHASE?/CN
L17 1 SEA FILE=REGISTRY ABB=ON PLU=ON CHOLESTEROL/CN
L21 1 SEA FILE=REGISTRY ABB=ON PLU=ON 83-46-5/RN
L22 4310 SEA FILE=HCAPLUS ABB=ON PLU=ON (L2 OR L21) AND (L17 OR CHOLESTEROL?)
L23 76 SEA FILE=HCAPLUS ABB=ON PLU=ON L22 AND (L5 OR L12 OR SQUALENE SYNTHASE OR (HMG OR HYDROXYMETHYLGLUTARYL OR HYDROXY(2W)(METHYLGLUTARYL OR (ME OR METHYL)(2W)GLUTARYL) OR HYDROXYMETHYL(2W)GLUTARYL)(W)((CO ENZYME OR COENZYME)(W)A OR COA) OR HMGCOA OR (POLYG? OR P)(W)MULTIFLOR?)
L24 20 SEA FILE=HCAPLUS ABB=ON PLU=ON L23 AND (L7 OR ACYL(W)(COA OR (COENZYME OR CO ENZYME)(W)A) OR HYDROXYLASE OR (CHRYSANT? OR C)(W)MORIFLOR?)

L25 4 L24 NOT L20

L25 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:691407 HCAPLUS
DOCUMENT NUMBER: 135:357299

09/726308

TITLE: Plant stanol fatty acid esters inhibit **cholesterol** absorption and hepatic **hydroxymethyl glutaryl coenzyme A** reductase activity to reduce plasma levels in rabbits

AUTHOR(S): Xu, Guorong; Salen, Gerald; Shefer, Sarah; Tint, G. Stephen; Nguyen, Lien B.; Batta, A. K.; Pcolinsky, Mark

CORPORATE SOURCE: Veterans Affairs Medical Center, Medical Service, East Orange, NJ, USA

SOURCE: Metabolism, Clinical and Experimental (2001), 50(9), 1106-1112
CODEN: METAAJ; ISSN: 0026-0495

PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aim of this study was to study the inhibitory effect of dietary stanols (campestanol and sitostanol) fatty acid esters (SE) on intestinal **cholesterol** absorption. New Zealand white rabbits were fed regular chow alone or enriched with 0.2% **cholesterol**, 0.33% SE + **cholesterol**, 0.66% SE + **cholesterol**, 1.2% SE + **cholesterol**, 2.4% SE + **cholesterol**, and 1.2% SE alone. After 2 wk, plasma **cholesterol** levels increased 3.6 times in the **cholesterol** group and did not decrease after addn. of 0.33% or 0.66% SE to the **cholesterol**-enriched diets. However, after addn. of 1.2% SE to the **cholesterol** diet, plasma **cholesterol** concn. decreased 50% ($P < .001$), but it did not decrease further after doubling of SE to 2.4%. Percent **cholesterol** absorption measured by the plasma dual-isotope ratio method was 73.0% .+-. 8.1% in the **cholesterol** group, which was similar to untreated baseline control. The percent absorption of **cholesterol** did not decrease significantly after addn. of 0.33% or 0.66% SE to the **cholesterol** diet but decreased 43.8% ($P < .001$) in the 1.2% SE + **cholesterol** group, a finding similar to those in rabbits fed 1.2% SE alone. Increasing SE to 2.4% in the **cholesterol** diet did not further decrease absorption. Hepatic **hydroxymethyl glutaryl CoA** (**HMG-CoA**) reductase activity reflecting **cholesterol** synthesis and low-d. lipoprotein receptor-mediated binding unexpectedly decreased 67% ($P < .01$) and 57% ($P < .05$) in rabbits fed 1.2% SE alone. Increasing dietary SE intake to 1.2% reduced **cholesterol** absorption and plasma levels. Dietary SE intake below 1.2% was ineffective and above 2.4% did not further decrease percent absorption or plasma **cholesterol** levels. These results support the hypothesis that dietary SEs competitively displace **cholesterol** from intestinal micelles to reduce **cholesterol** absorption and decrease plasma **cholesterol** levels.

IT **57-88-5, Cholesterol**, biological studies
83-46-5 37250-24-1, Hydroxymethyl glutaryl coenzyme A reductase
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(plant stanol fatty acid esters effect on **cholesterol** absorption and hepatic **hydroxymethyl glutaryl**

CoA reductase activity to reduce plasma levels in rabbits)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:442984 HCAPLUS
DOCUMENT NUMBER: 135:180195

TITLE: Dietary plant stanol esters reduce VLDL **cholesterol** secretion and bile saturation in apolipoprotein E*3-Leiden transgenic mice

AUTHOR(S): Volger, Oscar L.; Van der Boom, Hans; De Wit, Elly C. M.; Van Duyvenvoorde, Wim; Hornstra, Gerard; Plat, Jogchum; Havekes, Louis M.; Mensink, Ronald P.; Princen, Hans M. G.
CORPORATE SOURCE: Department of Human Biology, Maastricht University, Maastricht, 6200 MD, Neth.

SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology (2001), 21(6), 1046-1052
CODEN: ATVBFA; ISSN: 1079-5642
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Dietary plant stanols decrease blood serum **cholesterol** levels in humans and in hyperlipidemic rodents mainly by inhibiting intestinal **cholesterol** absorption. Female apolipoprotein E*3-Leiden transgenic mice were used to investigate the consequences of this effect on serum lipid levels and hepatic lipid metab. Five groups of 6-7 mice were fed for 9 wk diets contg. 0.25% **cholesterol** and 0 (control), 0.25, 0.5, 0.75, or 1.0% plant stanol (88% sitostanol, 10% campestanol) fatty acid esters. Compared with the control diet, plant stanol ester diets dose-dependently decreased blood serum **cholesterol** levels by 10-33%, mainly in very-low-d. lipoproteins (VLDL), intermediate-d. lipoproteins, and low-d. lipoproteins. The 1.0% stanol diet decreased the liver contents of cholesteryl esters by 62%, free **cholesterol** by 31%, and triglycerides by 38%, but did not change the hepatic VLDL-triglyceride and VLDL-apolipoprotein B prodn. rates. The stanol diets decreased the amts. of cholesteryl esters and free **cholesterol** incorporated in nascent VLDL by 72 and 30%, resp., resulting in a net 2-fold decreased VLDL-**cholesterol** output. Liver mRNA levels of low-d. lipoprotein receptors, 3-**hydroxy**-3-**methylglutaryl CoA** synthase, **cholesterol** 7.alpha.-**hydroxylase**, and sterol 27-**hydroxylase** were not changed by the stanol ester feeding. The serum lathosterol/**cholesterol** ratio was increased by 23%, indicating that dietary plant stanol esters increased the whole-body **cholesterol** synthesis. The stanol esters also decreased the **cholesterol** satn. index in bile by 55%. Thus, in apolipoprotein E*3-Leiden transgenic mice, dietary plant stanol esters dose-dependently lowered blood serum **cholesterol** levels via decreased secretion of VLDL-**cholesterol**. This was caused by decreased hepatic **cholesterol** content that also led to decreased biliary **cholesterol** output, indicative of decreased lithogenicity of bile in these mice.

IT **83-46-5**, .beta. **Sitosterol**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(dietary plant stanol fatty acid esters decrease liver VLDL-**cholesterol** secretion and bile satn. in apolipoprotein E*3-Leiden transgenic mice)

IT **57-88-5**, **Cholesterol**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); FFD (Food or feed use); BIOL (Biological study); PROC (Process); USES (Uses)
(dietary plant stanol fatty acid esters decrease liver VLDL-**cholesterol** secretion and bile satn. in apolipoprotein E*3-Leiden transgenic mice)

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:790868 HCAPLUS
DOCUMENT NUMBER: 134:28794
TITLE: Corn husk oil lowers plasma LDL **cholesterol** concentrations by decreasing **cholesterol** absorption and altering hepatic **cholesterol** metabolism in guinea pigs
AUTHOR(S): Ramjiganesh, Tripurasundari; Roy, Suheeta; Nicolosi, Robert J.; Young, Tracy L.; McIntyre, Jonathan C.; Fernandez, Maria Luz
CORPORATE SOURCE: Department of Nutritional Sciences, University of Connecticut, Storrs, CT, 06269, USA
SOURCE: Journal of Nutritional Biochemistry (2000), 11(7/8), 358-366
CODEN: JNBIEL; ISSN: 0955-2863
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To test the hypocholesterolemic mechanisms of corn husk oil (CoHO), male Hartley guinea pigs were fed diets with 0 (control), 5, 10, or 15 g CoHO and 0.25 g **cholesterol**/100 g feed. A pos. control group (LC) with low dietary **cholesterol** (0.04 g/100 g) was also used. Fat was adjusted to 15 g/100 g in all diets by the addn. of regular corn oil. Blood plasma low-d. lipoprotein (LDL) **cholesterol** concns. were 32, 55, and 57% lower with increasing doses of CoHO. The intake of CoHO resulted in 32-43% lower hepatic total and esterified **cholesterol** and 55-60% lower triacylglycerol concns. compared with the controls. CoHO intake resulted in plasma and hepatic **cholesterol** concns. similar to those in guinea pigs from the LC group. The no. of cholesteryl ester and free **cholesterol** mols. was higher in LDL from the control group than in LDL from the CoHO or LC groups. The hepatic .beta.-**hydroxy**-.beta.-**methylglutaryl**-**CoA** reductase activity was not modified by the CoHO intake, whereas **cholesterol** 7.alpha.-**hydroxylase** was up-regulated by 45-49% in the 10 and 15 g CoHO/100 g groups. The hepatic **acyl-CoA cholesterol** acyltransferase activity was down-regulated in a dose-dependent manner by 54, 58, and 63% with increasing doses of CoHO. The CoHO intake increased the fecal **cholesterol** excretion by 40-55%

compared with the control and LC groups. The total fecal neutral sterol excretion was enhanced 42-55% by CoHO compared with controls and by 59-68% compared with the LC group. Thus, CoHO exerts its hypocholesterolemic effect by decreasing **cholesterol** absorption and increasing bile acid output. These alterations in the intestinal lumen then alter hepatic **cholesterol** metab. and may affect the synthesis and catabolism of lipoproteins.

IT **83-46-5 9028-35-7**, .beta.-**Hydroxy**-.beta.-**methylglutaryl-CoA** reductase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(dietary corn husk oil lowers blood plasma LDL-**cholesterol** concns. by decreasing **cholesterol** absorption and altering hepatic **cholesterol** metab. in guinea pigs)

IT **57-88-5**, **Cholesterol**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); FFD (Food or feed use); BIOL (Biological study); PROC (Process); USES (Uses)
(dietary corn husk oil lowers blood plasma LDL-**cholesterol** concns. by decreasing **cholesterol** absorption and altering hepatic **cholesterol** metab. in guinea pigs)

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:405546 HCAPLUS
DOCUMENT NUMBER: 119:5546
TITLE: Regulation of **cholesterol** absorption in epithelial cells of human and rat small intestine
AUTHOR(S): Safonova, I. G.; Sviridov, D. D.; Rampal, P.; Nano, J. L.; Pavilov, M. Yu.; Repin, V. S.
CORPORATE SOURCE: Inst. Exp. Cardiol., Moscow, Russia
SOURCE: Biokhimiya (Moscow) (1993), 58(2), 274-84
CODEN: BIOHAO; ISSN: 0320-9725
DOCUMENT TYPE: Journal
LANGUAGE: Russian

AB **Cholesterol** absorption in human small intestine organ culture and rat small intestine epithelial cell culture IRD-98 was studied using [14C]**cholesterol**, [3H]**cholesterol**, and [14C]sitoserol. **Cholesterol** absorption is a dose- and time-dependent process, whereas **sitosterol** absorption is not and makes up to .apprx.25% of the total **cholesterol** absorption. **Cholesterol** absorption appeared to be a specific process. The endocytosis inhibitor monensin decreased specific **cholesterol** absorption by 37%.
Cholesterol absorption was examd. under different conditions influencing **cholesterol** metab. in the cell. Loading of IRD-98 cells with non-lipoprotein **cholesterol** caused a dose-dependent decrease of **cholesterol** absorption. The inhibitor of **acyl CoA:cholesterol** acyl transferase, compd. Sandox 58-035, had a similar effect on **cholesterol** absorption. Lovastatin, an inhibitor of 3-**hydroxymethyl**-3-**glutaryl CoA** reductase, stimulated **cholesterol** absorption in a dose-dependent

manner. Loading of cells with **cholesterol**, lovastatin, and Sandoz 58-035 had no effect on **sitosterol** absorption. The possibility was demonstrated of using human small intestine organ culture and rat small intestine epithelial cell culture IRD-98 as models for studying **cholesterol** absorption.

IT **57-88-5, Cholesterol**, biological studies
RL: BIOL (Biological study)
(absorption of, in small intestine epithelial cells of humans and lab. animals, regulation of)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, USTST=EPLUS, JAPIO' ENTERED AT 12:51:57 ON 25 OCT 2002)
L26 68 S L24
L27 36 DUP REM L26 (32 DUPLICATES REMOVED)

L27 ANSWER 1 OF 36 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-479986 [51] WPIDS
DOC. NO. CPI: C2002-136636
TITLE: Composition useful in food product, comprises **phytosterol** and/or phytostanol and/or soluble fiber, composition capable of inhibiting **cholesterol** biosynthesis and composition capable of increasing **cholesterol** metabolism.
DERWENT CLASS: B05 D13
INVENTOR(S): DE BONT, H B A; LANSINK, M; QI, C; VAN DER ZEE, L; VAN NORREN, K; CHEN, Q; VAN DER BURGT, L M J
PATENT ASSIGNEE(S): (DBON-I) DE BONT H B A; (LANS-I) LANSINK M; (QICC-I) QI C; (VZEE-I) VAN DER ZEE L; (VNOR-I) VAN NORREN K; (NUTR-N) NUTRICIA NV
COUNTRY COUNT: 99
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002043506	A2	20020606	(200251)*	EN	20
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
US 2002068095	A1	20020606	(200251)		
AU 2002016470	A	20020611	(200264)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002043506	A2	WO 2001-NL866	20011129
US 2002068095	A1	US 2000-726308	20001201
AU 2002016470	A	AU 2002-16470	20011129

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2002016470 A Based on WO 200243506

PRIORITY APPLN. INFO: US 2000-726308 20001201
AN 2002-479986 [51] WPIDS
AB WO 200243506 A UPAB: 20020812
NOVELTY - A composition (I) comprises:
(a) at least one **phytosterol** and/or phytostanol capable of reducing **cholesterol** absorption in the intestine and/or at least one soluble fiber capable of inhibiting ileal bile acid absorption;
(b) a composition capable of inhibiting **cholesterol** biosynthesis; and
(c) a composition capable of increasing **cholesterol** metabolism.
At least one of (b) and (c) is derived from plants.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for reducing serum **cholesterol** levels or preventing elevated blood serum **cholesterol** levels involving administering:
(a) at least one **phytosterol** and/or phytostanol (at least 10 mg/day) capable of reducing **cholesterol** absorption in the intestine, and/or at least one soluble fiber (at least 200 mg/day) capable of inhibiting ileal bile acid absorption;
(b) a plant-derived composition capable of inhibiting **cholesterol** biosynthesis; and
(c) a plant-derived composition capable of increasing **cholesterol** metabolism.
ACTIVITY - Anticholesterol. No test data provided.
MECHANISM OF ACTION - **HMG-CoA** -Reductase-Inhibitor; **Squalene-Synthase** -Inhibitor. No test data provided.
USE - In food or beverage products, nutritional supplements, tablets, capsules, microbeads, emulsions, powders, granules, suspensions, syrups, elixirs and chewing gums and for reducing serum **cholesterol** levels or preventing elevated blood serum **cholesterol** levels (claimed).
ADVANTAGE - The composition can be administered for a longer period and avoids the potential side effects or compensatory effects associated with the administration of relatively high levels of components solely directed at reducing **cholesterol** absorption in the intestine or at inhibiting **cholesterol** synthesis or at increasing **cholesterol** metabolism or at only two of these three mechanisms.
Dwg.0/0

L27 ANSWER 2 OF 36 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-241560 [29] WPIDS
DOC. NO. CPI: C2002-072652
TITLE: New N-substituted indoles useful in the treatment of e.g. non-insulin dependent diabetes mellitus, hyperglycemia and dyslipidemia.
DERWENT CLASS: B02
INVENTOR(S): ACTON, J J; BLACK, R M; JONES, A B; WOOD, H B
PATENT ASSIGNEE(S): (ACTO-I) ACTON J J; (BLAC-I) BLACK R M; (JONE-I) JONES A B; (WOOD-I) WOOD H B; (MERI) MERCK & CO INC
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002008188	A1	20020131	(200229)*	EN	73

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

US 2002042441 A1 20020411 (200231)
AU 2001077056 A 20020205 (200236)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002008188	A1	WO 2001-US22979	20010720
US 2002042441	A1 Provisional	US 2000-220778P	20000725
		US 2001-912961	20010725
AU 2001077056	A	AU 2001-77056	20010720

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001077056	A Based on	WO 200208188

PRIORITY APPLN. INFO: US 2000-220778P 20000725; US 2001-912961 20010725

AN 2002-241560 [29] WPIDS

AB WO 200208188 A UPAB: 20020508

NOVELTY - N-substituted indoles (I), their salts or prodrugs are new.

DETAILED DESCRIPTION - N-substituted indoles of formula (I), their salts or prodrugs are new.

R1 = methyl (optionally mono-, di- or tri-substituted by F);

R2 - R4 = H, halo, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-8C cycloalkyl, aryl, O(1-6C)alkyl, O(2-6C)alkenyl, O(2-6C)alkynyl, O-aryl, OH, S(1-6C)alkyl, S(2-6C)alkenyl, S(2-6C)alkynyl, SO2(1-6C)alkyl, SO2(2-6C)alkenyl, SO2(2-6C)alkynyl, OCON(R5)2, OCO(1-6C)alkyl or CN (where alkyl, alkenyl and alkynyl are optionally linear or branched and alkyl, alkenyl, alkynyl, cycloalkyl and aryl are optionally mono- to penta-substituted with halo, aryl, O-aryl or OMe);

R5, R6 = H, F, OH or 1-5C alkyl; or

C(R5+R6) = 3-6C cycloalkyl;

R7, R8 = H, F or 1-5C alkyl; or

R7+R8 = 3-6C cycloalkyl;

R9 = H or optionally linear or branched 1-5C alkyl;

Ar1 = phenyl, 1-naphthyl, 2-naphthyl, pyridyl or quinolyl (all mono-, di- or tri-substituted with R4);

X = C(O), S(O)2, CH2, CH(CH3), C(CH3)2, CF2 or cyclopropylidene;

Y = O or S; and

n = 0 - 5.

An INDEPENDENT CLAIM is also included for a pharmaceutical composition comprising (I), a carrier and at least one compound

selected from:

(a) insulin sensitizers including:

(i) peroxisome proliferator activated receptor gamma (PPAR gamma) agonists, such as glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555 and rosiglitazone), and compounds disclosed in WO97/27857, WO97/28115, WO97/28137 and WO97/27847;

(ii) biguanides such as metformin and phenformin;

(iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors; and

(iv) dipeptidyl peptidase IV (DP-IV) inhibitors;

(b) insulin or insulin mimetics;

(c) sulfonylureas such as tolbutamide and glipizide, or related materials;

(d) alpha -glucosidase inhibitors (such as acarbose);

(e) **cholesterol** lowering agents such as:

(i) **HMG-CoA** reductase inhibitors (preferably lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, ZD-4522 or other statins);

(ii) sequestrants (preferably cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran);

(iii) nicotinyl alcohol, nicotinic acid or its salt;

(iv) PPAR alpha agonists such as fenofibric acid derivatives (preferably gemfibrozil, clofibrate, fenofibrate or benzafibrate);

(v) PPAR alpha / gamma dual agonists, such as KRP-297;

(vi) inhibitors of **cholesterol** absorption, such as for example beta-**sitosterol**;

(vii) acyl CoA:cholesterol acyltransferase inhibitors, such as for example avasimibe, and

(viii) anti-oxidants, such as probucol;

(f) PPAR delta agonists such as those disclosed in WO97/28149;

(g) antiobesity compounds such as fenfluramine, dexfenfluramine, phentiramine, sulbitramine, orlistat, neuropeptide Y5 inhibitors, and beta 3 adrenergic receptor agonists;

(h) an ileal bile acid transporter inhibitor; and

(i) agents intended for use in inflammatory conditions such as aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclooxygenase- 2 selective inhibitors.

ACTIVITY - Antidiabetic; Anorectic; Antilipemic; Antiarteriosclerotic; Antiinflammatory; Antiulcer; Neuroprotective; Cytostatic; Antipsoriatic; Hypotensive; Ophthalmological; Vasotropic; Nootropic; Antitumor; Antianginal; Cardiant; Cerebroprotective.

MECHANISM OF ACTION - PPAR gamma agonist.

Test details are described but no results given.

USE - For treating, controlling or preventing at least one disease, disorder or condition e.g. noninsulin dependent diabetes mellitus, hyperglycemia, low glucose tolerance, insulin resistance, obesity, lipid disorders, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels, high LDL levels, atherosclerosis and its sequelae, vascular restenosis, irritable bowel syndrome, inflammatory bowel disease including Crohn's disease and ulcerative colitis, other inflammatory conditions, pancreatitis, abdominal obesity, neurodegenerative disease, retinopathy, neoplastic conditions, adipose cell tumors, adipose cell carcinomas, such as liposarcoma, prostate cancer and other cancers, including gastric, breast, bladder and colon cancers, angiogenesis, Alzheimer's disease, psoriasis, high blood pressure, Syndrome X, ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component (all

claimed); for treating angina, claudication, heart attack and stroke.

ADVANTAGE - (I) is free of some of the side effects that have been found in many of the glitazones.

Dwg.0/0

L27 ANSWER 3 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002092539 EMBASE
TITLE: Future outlook: Changing perspectives on best practice.
AUTHOR: Rader D.J.
SOURCE: Cardiology Review, (2002) 19/2 SUPPL. (24-28).
Refs: 5
ISSN: 1092-6607 CODEN: CARRFT
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The guidelines recently released by the National **Cholesterol** Education Program call for more aggressive lowering of the level of low-density lipoprotein (LDL) **cholesterol** and a significant increase in the number of patients eligible for therapy that lowers the level of LDL. Despite the efficacy of statins in lowering the LDL level and in reducing the risk of a coronary event or stroke, other **cholesterol**-lowering therapies are needed. Some patients are unable to tolerate statins or are not candidates for statin therapy because of liver enzyme abnormalities, age, a preference for nonsystemic therapy, or a modestly elevated LDL level. For those patients, bile acid sequestrants, intestinal bile acid transport inhibitors, **acyl coenzyme A:cholesterol** acyltransferase inhibitors, and a number of nonselective **cholesterol** absorption inhibitors are alternative treatments. However, those agents vary in their effectiveness in reducing the level of LDL. Their use often does not reduce the LDL level to the extent desired or is compromised by patients' poor compliance with therapy because of inconvenient dosing or unpleasant side effects. Ezetimibe, the first selective inhibitor of intestinal **cholesterol** absorption, is a promising alternative to the agents listed above. When ezetimibe is used either as monotherapy or in combination with a statin, once-daily dosing reduces the level of LDL by an average of 18%.

L27 ANSWER 4 OF 36 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-483029 [52] WPIDS
DOC. NO. CPI: C2001-144753
TITLE: New phosphonic acid derivatives, are useful as protein tyrosine phosphatase 1beta inhibitors for treating diabetes, obesity, atherosclerosis, inadequate glucose tolerance, insulin resistance or hyperlipidemia.
DERWENT CLASS: B05
INVENTOR(S): DUFRESNE, C; GAUTHIER, J Y; LAU, C K; LEBLANC, Y; LI, C S; ROY, P; SCHEIGETZ, J; THERIEN, M; WANG, Z
PATENT ASSIGNEE(S): (MERI) MERCK FROSST CANADA & CO; (MERI) MERCK

FROSST CANADA INC; (DUFR-I) DUFRESNE C; (GAUT-I) GAUTHIER J Y; (LAUC-I) LAU C K; (LEBL-I) LEBLANC Y; (LICS-I) LI C S; (ROYP-I) ROY P; (SCHE-I) SCHEIGETZ J; (THER-I) THERIEN M; (WANG-I) WANG Z

COUNTRY COUNT: 94

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001046206	A1	20010628	(200152)*	EN	101
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001023360	A	20010703	(200164)		
US 2002058644	A1	20020516	(200237)		
EP 1244678	A1	20021002	(200265)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2001046206	A1		WO 2000-CA1550	20001221
AU 2001023360	A		AU 2001-23360	20001221
US 2002058644	A1	Provisional	US 1999-171520P	19991222
			US 2000-745211	20001221
EP 1244678	A1		EP 2000-986935	20001221
			WO 2000-CA1550	20001221

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001023360	A	Based on	WO 200146206
EP 1244678	A1	Based on	WO 200146206

PRIORITY APPLN. INFO: US 1999-171520P 19991222; US 2000-745211 20001221

AN 2001-483029 [52] WPIDS

AB WO 200146206 A UPAB: 20010914

NOVELTY - Protein tyrosine phosphatase 1B inhibitor phosphonic acid derivatives and their salts and prodrugs are new.

- DETAILED DESCRIPTION - Protein tyrosine phosphatase 1B inhibitor phosphonic acid derivatives of formula (I) and their salts and prodrugs are new.

R1, R2 = 1-10C alkyl-(Ra)0-7, 2-10C alkenyl-(Ra)0-7, aryl-(Ra)0-3 or Het-(Ra)0-3;

Ra = aryl, OH, CN, halo, COOH, 1-6C alkyloxycarbonyl, 1-6C (halo)alkoxy, 1-6C (halo)alkyl, O-(1-10C alkylene)-COOH, aryloxy, 0-6C alkylene-SO3H, 0-6C alkylene-COOH, 0-6C alkylene-COO-(1-6C alkyl), 0-6C alkylene-COO-(2-6C alkenyl), 0-6C alkylene-CO-(1-6C alkyl), CONR3'R4', NR3'R4', SOy-(1-6C alkyl), SOyNR3'R4' or Het in which Het, aryl, alkyl and alkenyl are all optionally substituted by

1-3 halo, 1-6C (halo)alkyl, COOH, COO-(1-6C alkyl), 1-10C alkoxy, OH, Het or aryl, where Het and aryl are optionally substituted by 1-2 halo, 1-3C alkyl, 1-3C alkoxy, CF3 or OCF3;
y = 0 to 2;
aryl = 6-14 carbocyclic aromatic ring system comprising 1-3 fused phenyl rings;
Het = 5- to 10-membered aromatic ring system comprising 1 or 2 fused rings, 1-4 heteroatoms up to 4 of which are N-atoms and up to 2 O or SOy and 0-2 carbonyl groups;
Y, Z1, Z2 = -(CR3R4)a-X-(CR3R4)b-;
a + b = 0 -2;
X = a bond, O, SOy, NR3', CO, OCO, COO, CONR3', NR3'CO or CH=CH;
R3, R4 = H, halo or 1-3C (halo)alkyl;
R3' = H, 1-6C (halo)alkyl, OH, CO-(1-6C alkyl), CO-aryl, CO-Het, CO-(1-6C haloalkyl), aryl or Het;
R4' = H, 1-6C (halo)alkyl, aryl or Het;
W1 = H, OH, CN, halo, O-(1-6C alkyl)-(Ra)0-3, SOy-(1-6C alkyl)-(Ra)0-3, SO3H, 1-6C alkyl-(Ra)0-3, 1-6C haloalkyl-(Ra)0-3, COOH, COO-(1-6C (halo)alkyl)-(Ra)0-3, COO-(2-6C alkenyl)-(Ra)0-3, CO-(1-6C alkyl)-(Ra)0-3, CONR3'R4', SOyNR3'R4', NR3'R4', aryl or Het in which aryl and Het are optionally substituted by 1-3 halo, 1-6C (halo)alkyl, COOH, COO-(1-6C alkyl), 1-6C (halo)alkyloxy or OH or W1-C-C-W1 = fused phenyl ring.

INDEPENDENT CLAIMS are included for:
(1) compositions comprising (I),
(2) a carrier; and
(3) a compound selected from;
(a) insulin sensitizers comprising
(i) PPAR gamma agonists such as glitazone (e.g. troglitazone, pioglitazone, englitazone, MCC-555 or rosiglitazone);
(ii) biguanides such as meformin or phenformin;
(b) insulin or insulin mimetics;
(c) sulfonylureas such as tolbutamide or glipizide or related materials;
(d) alpha -glucosidase inhibitors (such as acarbose);
(e) **cholesterol** lowering agents such as
(i) **HMG-CoA** reductase inhibitor (lovastatin, simvastatin or pravastatin, fluvastatin, atorvastatin, rivastatin, or other stains)
(ii) sequestrants (cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran);
(iii) nicotinyl alcohol, nicotinic acid or salt;
(iv) PPAR alpha agonist such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate or benzafibrate);
(v) inhibitors of cholesterol absorption such as beta -sitosterol or (acyl CoA:cholesterol acyltransferase) inhibitors such as melinamide;
(vi) probucol;
(f) PPAR alpha / gamma agonists;
(g) antiobesity compounds such as appetite suppressants, fenfluramine, dexfenfluramine, phentiramine, sulbitramine, orlistat, neuropeptide Y5 inhibitors (NP Y5 receptor antagonists), leptin, which is a peptidic hormone, beta 3 adrenergic receptor agonist, PPAR gamma antagonists, or partial agonists;
(h) ileal bile acid transporter inhibitors;
(i) insulin receptor activators; and
(4) a compound of formula (II) or its salt:

OG = is not OH, where OG is converted to OH under physiological conditions during or after administration to yield a phosphonic acid;

G = phenyl, CHR'OC(=O)R'', or the second G is also selected from H;

R' = H or 1-6C alkyl; and

R'' = 1-6C alkyl, or 1-6C alkoxy (all optionally substituted by 1-5 halo, phenyl, where phenyl is optionally substituted by 1-3 of halo, CH3, CF3, OCH3 or OCF3);

ACTIVITY - Antidiabetic; anorectic; antiarteriosclerotic; antilipemic; vasotropic; antiinflammatory; cytostatic.

No specific biological data given.

MECHANISM OF ACTION - Protein tyrosine phosphatase 1 beta inhibitor.

USE - (I) are useful for treating type 1 diabetes, type 2 diabetes, inadequate glucose tolerance, insulin resistance, obesity, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels, atherosclerosis, vascular restenosis, inflammatory bowel disease, pancreatitis, adipose cell tumors, adipose cell carcinoma, liposarcoma, dyslipidemia, cancer or neurodegenerative disease (claimed).

Dwg.0/0

L27 ANSWER 5 OF 36 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:836258 SCISEARCH
THE GENUINE ARTICLE: 481UL
TITLE: Macrophage 3-**hydroxy**-3-**methylglutaryl coenzyme A** reductase activity in sitosterolemia: Effects of increased cellular **cholesterol** and **sitosterol** concentrations
AUTHOR: Nguyen L B (Reprint); Salen G; Shefer S; Tint G S; Ruiz F
CORPORATE SOURCE: Univ Med & Dent New Jersey, New Jersey Med Sch, Dept Med, Ctr Liver, 185 S Orange Ave, MSB H-532, Newark, NJ 07103 USA (Reprint); Univ Med & Dent New Jersey, New Jersey Med Sch, Dept Med, Ctr Liver, Newark, NJ 07103 USA; Univ Med & Dent New Jersey, New Jersey Med Sch, Dept Med, Div Gastroenterol, Newark, NJ 07103 USA; New Jersey Vet Affairs Med Ctr, Gastroenterol Res Lab, E Orange, NJ USA
COUNTRY OF AUTHOR: USA
SOURCE: METABOLISM-CLINICAL AND EXPERIMENTAL, (OCT 2001) Vol. 50, No. 10, pp. 1224-1229.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA.
ISSN: 0026-0495.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 29

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Sitosterolemia is a rare, recessively inherited disease characterized clinically by accelerated atherosclerosis and xanthomas and biochemically by hyperabsorption and retention of **sitosterol** and other plant sterols in tissues. Decreased **cholesterol** biosynthesis and inhibition of 3-hydroxy-3-methylgluratyl coenzyme A (**HMG-CoA**)

reductase and other enzymes in the biosynthetic pathway have been associated with enhanced low-density lipoprotein (LDL) receptor function. We examined the effects of **cholesterol** and **sitosterol** on sterol concentrations and composition and **HMG-CoA** reductase activity in monocyte-derived macrophages (MDM) from 12 control and 3 homozygous sitosterolemic subjects. The cells were cultured up to 7 days in media devoid of plant sterols, but containing increasing amounts of serum **cholesterol**. Before culture, MDM from the homozygous sitosterolemic subjects contained 22% more total sterols than cells from control subjects. Plant sterols and stanols represented 15.6% of MDM total sterols in sitosterolemic cells, but only 3.8% in control cells. After 7 days of culture in 10% delipidated serum (DLS) (20 mug/mL **cholesterol**, no **sitosterol**), all plant sterols were eliminated so that cells from both phenotypes contained only **cholesterol**. When DLS was replaced with fetal bovine serum (FBS) (300 mug/mL **cholesterol**), with and without addition of 200 mug/mL LDL, **cholesterol** levels in MDM from sitosterolemic subjects increased 108% ($P < .05$) compared with a 65% increase ($P < .04$) in control MDM cultured similarly. MDM **HMG-CoA** reductase activity from the 3 sitosterolemic subjects, which was significantly lower than controls at baseline (24 +/- 3 v 60 +/- 10 pmol/mg/min, $P < .05$), was not downregulated by increased cellular **cholesterol** levels, as observed in control cells. Control MDM were also cultured in medium that contained 10% DLS and was supplemented with 100 mug/mL **cholesterol** or **sitosterol** dissolved in ethanol or the ethanol vehicle alone. In contrast to cellular **cholesterol** accumulation, which significantly downregulated **HMG-CoA** reductase activity (-53%, $P < .05$), the increase in cellular **sitosterol** up to 25.1% of total sterols did not change MDM **HMG-CoA** reductase activity. Evidence of a normal **HMG-CoA** reductase protein in sitosterolemic calls, which was not derepressed upon removal of cellular **sitosterol**, and the failure of cellular **sitosterol** to inhibit normal **HMG-CoA** reductase activity argue against feedback inhibition by **sitosterol** as a mechanism for low reductase activity in this disease. The larger accumulation of sterols and inadequate downregulation of **HMG-CoA** reductase in MDM may be mechanisms for foam cell formation and explain, in part, the increased risk of atherosclerosis in sitosterolemia.

L27 ANSWER 6 OF 36 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001507103 MEDLINE
DOCUMENT NUMBER: 21439673 PubMed ID: 11555847
TITLE: Plant stanol fatty acid esters inhibit **cholesterol** absorption and hepatic **hydroxymethyl glutaryl coenzyme A** reductase activity to reduce plasma levels in rabbits.
AUTHOR: Xu G; Salen G; Shefer S; Tint G S; Nguyen L B; Batta A K; Pcolinsky M
CORPORATE SOURCE: Medical Service, Veterans Affairs Medical Center, East Orange, NJ 07018-1095, USA.
CONTRACT NUMBER: DK26756 (NIDDK)
HL18094 (NHLBI)

SOURCE: METABOLISM: CLINICAL AND EXPERIMENTAL, (2001 Sep) 50 (9) 1106-12.
Journal code: 0375267. ISSN: 0026-0495.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010917
Last Updated on STN: 20011022
Entered Medline: 20011018

AB The aim of this study was to study the inhibitory effect of dietary stanols (campestanol and sitostanol) fatty acid esters (SE) on intestinal **cholesterol** absorption. New Zealand white rabbits were fed regular chow alone or enriched with 0.2% **cholesterol**, 0.33% SE + **cholesterol**, 0.66% SE + **cholesterol**, 1.2% SE + **cholesterol**, 2.4% SE + **cholesterol**, and 1.2% SE alone. After 2 weeks, plasma **cholesterol** levels increased 3.6 times in the **cholesterol** group and did not decrease after addition of 0.33% or 0.66% SE to the **cholesterol**-enriched diets. However, after addition of 1.2% SE to the **cholesterol** diet, plasma **cholesterol** concentration decreased 50% (P <.001), but it did not decrease further after doubling of SE to 2.4%. Percent **cholesterol** absorption measured by the plasma dual-isotope ratio method was 73.0% +/- 8.1 % in the **cholesterol** group, which was similar to untreated baseline control. The percent absorption of **cholesterol** did not decrease significantly after addition of 0.33% or 0.66% SE to the **cholesterol** diet but decreased 43.8% (P <.001) in the 1.2% SE + **cholesterol** group, a finding similar to those in rabbits fed 1.2% SE alone. Increasing SE to 2.4% in the **cholesterol** diet did not further decrease absorption. Hepatic **hydroxymethyl glutaryl coenzyme A** (**HMG-CoA**) reductase activity reflecting **cholesterol** synthesis and low-density lipoprotein receptor-mediated binding unexpectedly decreased 67% (P <.01) and 57% (P <.05) in rabbits fed 1.2% SE alone. Increasing dietary SE intake to 1.2% reduced **cholesterol** absorption and plasma levels. Dietary SE intake below 1.2% was ineffective and above 2.4% did not further decrease percent absorption or plasma **cholesterol** levels. These results support the hypothesis that dietary SEs competitively displace **cholesterol** from intestinal micelles to reduce **cholesterol** absorption and decrease plasma **cholesterol** levels.

L27 ANSWER 7 OF 36 MEDLINE - DUPLICATE 2
ACCESSION NUMBER: 2001329532 MEDLINE
DOCUMENT NUMBER: 21290587 PubMed ID: 11397718
TITLE: Dietary plant stanol esters reduce VLDL **cholesterol** secretion and bile saturation in apolipoprotein E*3-Leiden transgenic mice.
AUTHOR: Volger O L; van der Boom H; de Wit E C; van Duyvenvoorde W; Hornstra G; Plat J; Havekes L M; Mensink R P; Princen H M
CORPORATE SOURCE: TNO Prevention and Health, Leiden, the Netherlands.
SOURCE: ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY,

(2001 Jun) 21 (6) 1046-52.
Journal code: 9505803. ISSN: 1524-4636.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB Dietary plant stanols lower serum **cholesterol** levels in humans and in hyperlipidemic rodents, mainly by inhibition of the intestinal **cholesterol** absorption. We used female apolipoprotein E*3-Leiden transgenic mice to investigate the consequences of this effect on serum lipid levels and hepatic lipid metabolism. Five groups of 6 or 7 mice received for 9 weeks a diet containing 0.25% **cholesterol** and 0.0%, 0.25%, 0.5%, 0.75%, or 1.0% (wt/wt) plant stanols (sitostanol 88% [wt/wt], campestanol 10% [wt/wt]) esterified to fatty acids. Compared with the control diet, plant stanol ester treatment dose-dependently reduced serum **cholesterol** levels by 10% to 33% ($P<0.05$), mainly in very low density lipoproteins (VLDLs), intermediate density lipoproteins, and low density lipoproteins. Furthermore, 1.0% of the dietary plant stanols significantly decreased the liver contents of cholesteryl esters (-62%), free **cholesterol** (-31%), and triglycerides (-38%) but did not change the hepatic VLDL-triglyceride and VLDL-apolipoprotein B production rates. However, plant stanol ester feeding significantly decreased the amounts of cholesteryl esters and free **cholesterol** incorporated in nascent VLDLs by 72% and 30%, respectively, resulting in a net 2-fold decreased VLDL **cholesterol** output. Liver mRNA levels of low density lipoprotein receptors, 3-**hydroxy**-3-**methylglutaryl coenzyme A** synthase, **cholesterol** 7alpha-**hydroxylase**, and sterol 27-**hydroxylase** were not changed by plant stanol ester feeding. Nevertheless, the serum lathosterol-to-**cholesterol** ratio was significantly increased by 23%, indicating that dietary plant stanol esters increased whole-body **cholesterol** synthesis. Plant stanol esters also significantly decreased the **cholesterol** saturation index in bile by 55%. In conclusion, in apolipoprotein E*3-Leiden transgenic mice, plant stanol ester feeding dose-dependently lowered serum **cholesterol** levels as a result of a reduced secretion of VLDL **cholesterol**. This was caused by a decreased hepatic **cholesterol** content that also resulted in a lowered biliary **cholesterol** output, indicative of a reduced lithogenicity of bile in these mice.

L27 ANSWER 8 OF 36 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001330168 MEDLINE
DOCUMENT NUMBER: 21291315 PubMed ID: 11398149
TITLE: Hepatic **cholesterol** and bile acid synthesis, low-density lipoprotein receptor function, and plasma and fecal sterol levels in mice: effects of apolipoprotein E deficiency and probucol or **phytosterol** treatment.
AUTHOR: Moghadasian M H; Nguyen L B; Shefer S; Salen G; Batta A K; Frohlich J J
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, St.

Paul's Hospital and University of British Columbia, Vancouver, BC, Canada.
CONTRACT NUMBER: DK 26756 (NIDDK)
SOURCE: METABOLISM: CLINICAL AND EXPERIMENTAL, (2001 Jun) 50 (6) 708-14.
Journal code: 0375267. ISSN: 0026-0495.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB We compared hepatic **cholesterol** metabolism in apolipoprotein (apo) E-knockout (KO) mice with their wild-type counterparts. We also investigated the effects of treatment with **phytosterols** or probucol on the activity of hepatic 3-**hydroxy**-3-**methyl-glutaryl coenzyme A** (**HMG-CoA**) reductase (**cholesterol** synthesis), **cholesterol** 7 alpha-**hydroxylase** and sterol 27-**hydroxylase** (bile acid synthesis), and low-density lipoprotein (LDL) receptor function in this animal model of atherogenesis. These findings were then related to treatment-induced changes in plasma, hepatic, and fecal sterol concentrations. Mouse liver membranes have binding sites similar to LDL receptors; the receptor-mediated binding represents 80% of total binding and is LDL concentration-dependent. These binding sites have higher affinity for apo E-containing particles than apo B only-containing particles. Deletion of apo E gene was associated with several-fold increases in plasma **cholesterol** levels, 1.5-fold increase in hepatic **cholesterol** concentrations, 50% decrease in **HMG-CoA** reductase activity, 30% increase in **cholesterol** 7 alpha-**hydroxylase** and 25% decrease in LDL receptor function. Treatment of apo E-KO mice with either probucol or **phytosterols** significantly reduced plasma **cholesterol** levels. **Phytosterols** significantly increased the activity of hepatic **HMG-CoA** reductase, and probucol significantly increased **cholesterol** 7 alpha-**hydroxylase** activity. Neither treatment significantly altered hepatic LDL receptor function. **Phytosterols**, but not probucol, significantly increased fecal sterol excretion and decreased hepatic **cholesterol** concentrations. Plasma **cholesterol** lowering effects of **phytosterols** and probucol are due to different mechanisms: stimulation of **cholesterol** catabolism via increased bile acid synthesis by probucol and decreased **cholesterol** absorption by **phytosterols**. In the absence of apo E, hepatic LDL receptors could not be upregulated and did not contribute to the **cholesterol** lowering effects of either agent.

L27 ANSWER 9 OF 36 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:218054 SCISEARCH
THE GENUINE ARTICLE: 407XG
TITLE: Feeding unsaponifiable compounds from rice bran oil does not alter hepatic mRNA abundance for

cholesterol metabolism-related proteins in hypercholesterolemic rats

AUTHOR: Nagao K; Sato M (Reprint); Takenaka M; Ando M; Iwamoto M; Imaizumi K

CORPORATE SOURCE: Kyushu Univ, Grad Sch, Fac Agr, Div Biosci & Biotechnol, Lab Nutr Chem, Fukuoka 8128581, Japan (Reprint)

COUNTRY OF AUTHOR: Japan

SOURCE: BIOSCIENCE BIOTECHNOLOGY AND BIOCHEMISTRY, (FEB 2001) Vol. 65, No. 2, pp. 371-377.
Publisher: JAPAN SOC BIOSCI BIOTECHN AGROCHEM, JAPAN ACAD SOC CTR BLDG, 2-4-6 YAYOI BUNKYO-KU, TOKYO, 113, JAPAN.
ISSN: 0916-8451.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 24

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The hypocholesterolemic effect of rice bran oil (RBO) is defined in human and animal experiments which indicate the presence of active component(s) in the unsaponifiable fraction, but the detailed mechanism is not known yet. Exogenously hypercholesterolemic (ExHC) rats were fed for 2 weeks on a 0.5% **cholesterol** diet supplemented with 10% each of RBO, RBO-simulated oil (RBOSO) in its fatty acid composition, or RBOSO plus 0.25% unsaponifiable compounds (UC) from RBO. Rats fed RBO or the UC resulted in lowing serum and liver **cholesterol** concentration and preventing reduction of high density lipoproteinic-**cholesterol**. Dietary RBO or the UC led to an elevation of fecal neutral sterol excretion, but no significant change in fecal bile acid excretion or in hepatic abundance of mRNAs for 3-**hydroxy**-3-**methylglutaryl** **-CoA** reductase, **cholesterol**-7 alpha - **hydroxylase**, and low density lipoprotein receptor. Besides, serum and liver alpha -tocopherol concentrations were lowered in RBO or the UC-fed rats. These results show that the UC in RBO leads to a decreased serum **cholesterol** concentration by interrupting the absorption of intestinal hydrophobic compounds rather than by modifying **cholesterol** metabolism in the liver.

L27 ANSWER 10 OF 36 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 2000467964 MEDLINE

DOCUMENT NUMBER: 20475664 PubMed ID: 11022827

TITLE: Effects of simvastatin on hepatic **cholesterol** metabolism, bile lithogenicity and bile acid hydrophobicity in patients with gallstones.

AUTHOR: Smith J L; Roach P D; Wittenberg L N; Riottot M; Pillay S P; Nestel P J; Nathanson L K

CORPORATE SOURCE: Department of Surgery, The University of Queensland, Royal Brisbane Hospital, Australia..
J.Smith@mailbox.uq.edu.au

SOURCE: JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY, (2000 Aug) 15 (8) 871-9.
Journal code: 8607909. ISSN: 0815-9319.

PUB. COUNTRY: Australia

DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010208

AB BACKGROUND AND AIMS: There is limited information available on the effects of 3-**hydroxy**-3-**methylglutaryl** **coenzyme A** reductase inhibitors on hepatic and biliary **cholesterol** metabolism in patients with gallstones. The aims of this study were to determine the effect of simvastatin on the regulatory elements of **cholesterol** metabolism that determine the concentrations of **cholesterol** in plasma and bile. METHODS: Thirty-one gallstone patients were enrolled in the study; 17 were treated with 20 mg simvastatin daily for 3 weeks prior to cholecystectomy and 14 served as controls. Samples of blood, liver, gall-bladder bile and bile from the common bile duct (CBD) were collected and analysed. RESULTS: The plasma **cholesterol** (-30%), triacylglycerol (-23%) and low-density lipoprotein (LDL) **cholesterol** (-42%) concentrations were significantly lowered by simvastatin treatment, as was the plasma lathosterol: **cholesterol** (-70%), which reflects whole-body **cholesterol** synthesis. Despite these changes, the hepatic LDL receptor protein and LDL receptor activity in circulating mononuclear cells were similar in both groups. There were no differences in the plasma **phytosterol**: **cholesterol** , which reflects the intestinal **cholesterol** absorption capacity or in the activity of hepatic **acyl-coenzyme A**: **cholesterol** acyltransferase. There were however, lower **cholesterol** concentrations in CBD (-68%) and gall bladder (-41%) bile, and decreased lithogenic (-47%) and bile acid hydrophobicity (-22%) indices of CBD bile in the simvastatin group. CONCLUSIONS: These data indicate that simvastatin reduced plasma and biliary **cholesterol** levels primarily by reducing **cholesterol** synthesis. The reduction in CBD bile lithogenicity and bile acid hydrophobicity by simvastatin suggests that this agent may be useful for people who have early stages of **cholesterol** gallstone development and in whom a choleretic effect is required.

L27 ANSWER 11 OF 36 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2000:819994 SCISEARCH
THE GENUINE ARTICLE: 367GK
TITLE: Corn husk oil lowers plasma LDL **cholesterol** concentrations by decreasing **cholesterol** absorption and altering hepatic **cholesterol** metabolism in guinea pigs
AUTHOR: Ramjiganesh T (Reprint); Roy S; Nicolosi R J; Young T L; McIntyre J C; Fernandez M L
CORPORATE SOURCE: UNIV CONNECTICUT, DEPT NUTR SCI, 3624 HORSEBARN RD EXTENS, STORRS, CT 06269 (Reprint); UNIV MASSACHUSETTS, DEPT CLIN SCI, LOWELL, MA; MONSANTO CO, ST LOUIS, MO
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF NUTRITIONAL BIOCHEMISTRY, (JUL-AUG 2000) Vol. 11, No. 7-8, pp. 358-366.
Publisher: ELSEVIER SCIENCE INC, 655 AVENUE OF THE AMERICAS, NEW YORK, NY 10010.
ISSN: 0955-2863.

DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; AGRI
LANGUAGE: English
REFERENCE COUNT: 52

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB To test the hypocholesterolemic mechanisms of corn husk oil (CoHO), male Hartley guinea pigs were fed diets containing increasing doses of CoHO, either 0 (control), 5, 10, or 15 g/100 g, and 0.25 g/100 g **cholesterol**. A positive control group (LC) with low dietary **cholesterol** (0.04 g/100 g) was also included. Fat was adjusted to 15 g/100 g in all diets by the addition of regular corn oil. Plasma low density lipoprotein (LDL) **cholesterol** concentrations were 32, 55, and 57% ($P < 0.0005$) lower with increasing doses of CoHO. In addition, intake of CoHO resulted in 32 to 43% lower hepatic total and esterified **cholesterol** and 55 to 60% lower triacylglycerol concentrations compared with the control group ($P < 0.01$). CoHO intake resulted in plasma and hepatic **cholesterol** concentrations similar to those in guinea pigs from the LC group. The number of cholesteryl ester and free **cholesterol** molecules was higher in LDL from the control group than in LDL from the CoHO or the LC groups. Hepatic beta **-hydroxy**-beta - **methylglutaryl-coenzyme A** reductase activity was not modified by CoHO intake whereas **cholesterol** 7 alpha **-hydroxylase** was up-regulated by 45 to 49% ($P < 0.01$) in the 10 and 15 g/100 g CoHO groups. Hepatic **acyl coenzyme A cholesterol** acyltransferase activity was down-regulated in a dose-dependent manner by 54, 58, and 63% with increasing doses of CoHO. CoHO intake resulted in increased fecal **cholesterol** excretion by 40 to 55% compared with the control and LC groups. Total fecal neutral sterol excretion was enhanced 42 to 55% by CoHO compared with the control group and by 59 to 68% compared with the LC group. The data from these studies suggest that CoHO has its hypocholesterolemic effect by decreasing **cholesterol** absorption and increasing bile acid input. These alterations in the intestinal lumen alter hepatic **cholesterol** metabolism and may effect the synthesis and catabolism of lipoproteins. (J. Nutr. Biochem. 11:358-366, 2000)

L27 ANSWER 12 OF 36 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1999-243579 [20] WPIDS
DOC. NO. NON-CPI: N1999-181297
DOC. NO. CPI: C1999-070962
TITLE: Reducing mammalian serum total **cholesterol** for treating hyperlipidemia, hypercholesterolemia and atherosclerosis.
DERWENT CLASS: B04 D13 D16 P14
INVENTOR(S): CHERUKURI, R S V; CHERUVANKY, R; LYNCH, I E; MCPEAK, P; LYNCH, I; QURESHI, A A
PATENT ASSIGNEE(S): (RICE-N) RICEX CO INC; (CHER-I) CHERUKURI R S V; (CHER-I) CHERUVANKY R; (LYNC-I) LYNCH I; (MCPE-I) MCPEAK P; (QURE-I) QURESHI A A; (RICE-N) RICEX CO
COUNTRY COUNT: 82
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG

WO 9911144 A1 19990311 (199920)* EN 40
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9892098 A 19990322 (199931)
US 6126943 A 20001003 (200050)
US 6350473 B1 20020226 (200220)
US 2002086069 A1 20020704 (200247)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9911144	A1		WO 1998-US17881	19980828
AU 9892098	A		AU 1998-92098	19980828
US 6126943	A	Provisional	US 1997-57870P	19970902
			US 1998-143159	19980828
US 6350473	B1	Provisional	US 1997-57870P	19970902
		Cont of	US 1998-143159	19980828
			US 2000-624474	20000724
US 2002086069	A1	Provisional	US 1997-57870P	19970902
		Cont of	US 1998-143159	19980828
		Div ex	US 2000-624474	20000724
			US 2001-992332	20011116

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9892098	A	Based on	WO 9911144
US 6350473	B1	Cont of	US 6126943

PRIORITY APPLN. INFO: US 1997-57870P 19970902; US 1998-143159 19980828; US 2000-624474 20000724; US 2001-992332 20011116

AN 1999-243579 [20] WPIDS

AB WO 9911144 A UPAB: 19990525
NOVELTY - Reducing mammalian serum total **cholesterol**, low density lipoprotein (LDL) **cholesterol**, apolipoprotein B and triglyceride levels, comprises ingesting a stabilized rice bran derivative obtained by enzyme treatment of rice bran, and/or an insolubilized fraction.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) preparing enzyme treated stabilized rice bran derivative comprising:

(a) mixing stabilized rice bran with an aqueous solution to form a 15-35% sold rice bran slurry;

(b) adding an enzyme to the slurry to convert starch to dextrin; and

(c) drying the slurry to obtain the stabilized rice bran derivative;

(2) the product of the preparation of (1); and

(3) a method for increasing the high density lipoprotein (HDL)/LDL **cholesterol** ratio in mammalian serum, comprising

ingesting a stabilized rice bran derivative obtained by enzyme treatment of rice bran, and/or an insolubilized fraction.

ACTIVITY - Antiarteriosclerotic; Antilipemic.

MECHANISM OF ACTION - The major bioactive components present in the rice bran derivatives are tocopherols, tocotrienols, gamma -oryzanol, **phytosterols**, polyphenols, inositol, B vitamins, protein, fiber, and fat. The components act mostly synergistically, e.g. by enzyme inhibitions: three enzymes, namely 3-**hydroxy**-3-**methylglutaryl-coenzyme A** (**HMGCoA**) reductase, **Acyl coenzyme A** transferase (ACAT) and esterase are inhibited. **HMGCoA** reductase, a key enzyme involved in the **cholesterol** biosynthesis is inhibited by the tocotrienols, post transcriptionally, reducing the synthesis of **cholesterol** resulting in low circulating **cholesterol**. **Acyl coenzyme A** transferase (ACAT), inhibition is brought about by:

(a) the prevention of cellular **cholesterol** esterification thereby enriching high density lipoprotein **cholesterol** (HDL) with free **cholesterol**;

(b) elevation of HDL, a positive effect, and decreased synthesis of very low density lipoprotein **cholesterol** (VLDL); and

(c) increased clearance of **cholesterol** as bile acids and bile salts.

The net result is lower circulating **cholesterol**. **Cholesterol** esterases are inhibited by cycloartenol, a component of -y-oryzanol, resulting in a slower hydrolysis of **cholesterol** esters and decreased absorption. This results in lower circulating total **cholesterol**. gamma -Oryzanol inhibits platelet aggregation, and aortic streaks thus reducing atherosclerosis. Rice bran derivatives contain a significant variety and concentration of antioxidants. Antioxidants such as tocopherols, tocotrienols, gamma -oryzanol, polyphenols as ferulic acid, and lipoic acid are involved in the repair of free radical damage, preventing low density lipoprotein **cholesterol** (LDL) oxidation, resulting in the reduction of vascular damage that can lead to cardiovascular disease. Cycloartenol, a component of gamma -oryzanol, has a structure similar to **cholesterol** and competes with receptor sites of **cholesterol**. This causes a sequestration of **cholesterol** as bile salts and bile pigments, thus maintaining lower levels of circulating **cholesterol**. **Phytosterols** and fiber facilitate **cholesterol** sequestration from the body through increased excretion of bile salts and bile acids, resulting in lower levels of circulating **cholesterol**. The protein, fat (with high levels of polyunsaturated and monounsaturated fatty acids), and B vitamins also contribute to the hypocholesterolemic effect.

USE - The method is used to treat subjects in which elevated levels of serum total **cholesterol**, LDL-**cholesterol**, VLDL-**cholesterol**, apolipoprotein B and triglyceride levels may lead to hyperlipidemia, cardiovascular disease, atherosclerosis, arteriosclerosis or xanthomatosis.

Dwg.0/0

L27 ANSWER 13 OF 36 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999190493 MEDLINE
DOCUMENT NUMBER: 99190493 PubMed ID: 10092072

TITLE: Histologic, hematologic, and biochemical characteristics of apo E-deficient mice: effects of dietary **cholesterol** and **phytosterols**.
AUTHOR: Moghadasian M H; Nguyen L B; Shefer S; McManus B M; Frohlich J J
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, St. Paul's Hospital and University of British Columbia, Vancouver, Canada.
CONTRACT NUMBER: DK 26758 (NIDDK)
SOURCE: LABORATORY INVESTIGATION, (1999 Mar) 79 (3) 355-64. Journal code: 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 19990426
Entered Medline: 19990413

AB In this study, we examined the effects of a "Western-type" diet containing 9% (w/w) fat and 0.15% (w/w) **cholesterol**, in the presence or absence of 2% (w/w) **phytosterol** mixture over an 18-week period in apolipoprotein E-deficient mice. Addition of **phytosterols** to the high **cholesterol** diet was associated with normalization of the depressed hepatic 3-**hydroxy**-3-**methylglutaryl-coenzyme** **A** reductase activity (from 22.3+/-6.3 to 55.4+/-19.9 pmol/mg protein/minutes, $p < 0.05$). This finding was associated with a significant decrease in plasma and hepatic **cholesterol** concentrations compared with animals fed the high **cholesterol** diet without **phytosterols** (33.3+/-5.0 versus 19.2+/-6.2 pmol/mg protein, $p < 0.05$). The activities of **cholesterol** 7alpha-**hydroxylase** and sterol 27-**hydroxylase** were comparable between the two groups of mice. Urinalyses and hematologic data were comparable between the two groups except for significantly lower platelet counts in the **phytosterol**-treated animals (681.6+/-118.9 versus 857.1+/-185.4 x10(9)/L, $p < 0.05$). The **phytosterol**-treated animals had significantly ($p < 0.05$) less fragile erythrocytes when exposed to 0.08, 0.07, or 0.05 M NaCl compared with **cholesterol**-fed mice. The consumption of the Western-type diet was associated with the development of xanthomatous skin lesions in 33% of the **cholesterol**-fed animals, but in none of the **phytosterol**-treated animals. Histologic examination revealed oil red O-negative vacuolation in liver and kidney parenchymal cells of the **cholesterol**-fed group, but not in the **phytosterol**-treated mice. Arrested spermatogenesis and atrophy of seminiferous tubules were observed, to a variable extent, in both groups of animals. We conclude that addition of the **phytosterol** mixture (2% w/w) to a Western-type diet in apolipoprotein E-deficient mice significantly decreases plasma and hepatic **cholesterol** concentrations, increases hepatic 3-**hydroxy**-3-**methylglutaryl-coenzyme** **A** reductase activity, and prevents cutaneous xanthomatosis and vacuolation in the parenchymal cells of kidneys and livers.

ACCESSION NUMBER: 1998272304 MEDLINE
DOCUMENT NUMBER: 98272304 PubMed ID: 9610773
TITLE: Sitosterolemia: exclusion of genes involved in reduced **cholesterol** biosynthesis.
AUTHOR: Patel S B; Honda A; Salen G
CORPORATE SOURCE: Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas 75235-9052, USA.
CONTRACT NUMBER: HL-17818 (NHLBI)
SOURCE: JOURNAL OF LIPID RESEARCH, (1998 May) 39 (5) 1055-61. Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980910
Last Updated on STN: 19980910
Entered Medline: 19980828

AB Sitosterolemia (phytosterolemia) is a rare autosomal recessively inherited disorder that is characterized by premature coronary artery disease, xanthomas, and increased plasma plant sterols and 5alpha-stanols. Affected individuals show an increased absorption of both **cholesterol** and **sitosterol** from the diet, decreased bile clearance of these sterols and their metabolites resulting in markedly expanded whole body **cholesterol** and **sitosterol** pools. Biochemical studies have shown that the regulation of the **cholesterol** biosynthetic pathway may be abnormal in this condition. In particular, the activities and mRNA for the biosynthetic enzymes, 3-**hydroxy**-3-**methylglutaryl coenzyme A** (**HMG-CoA**) reductase and **HMG-CoA** synthase are low in liver biopsy specimens isolated from affected individuals, suggesting replete intracellular **cholesterol** pools. However, the membrane expression of hepatocyte low density lipoprotein receptors was increased, suggesting discordant regulation. Segregation analyses in three families for the genes for **HMG-CoA** reductase, **HMG-CoA** synthase, and LDL-receptor excluded these as sites of mutation. In view of the previously described discordant regulation of the above genes in sitosterolemia, the two major regulatory genes for this pathway, sterol regulatory element binding proteins (SREBP-1 and -2), were also examined. These genes did not segregate with the disease and were thus excluded. Two other genes involved in **cholesterol** absorption and chylomicron secretion, namely **acyl coenzyme A:cholesterol** acyltransferase (ACAT) and microsomal triglyceride transfer protein (MTP) were also examined for segregation and similarly excluded. Although the gene defect in sitosterolemia therefore remains to be elucidated, important candidate genes have been excluded.

L27 ANSWER 15 OF 36 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 97:215469 SCISEARCH
THE GENUINE ARTICLE: WM242
TITLE: Effect of micellar beta-**sitosterol** on **cholesterol** metabolism in CaCo-2 cells
AUTHOR: Field F J (Reprint); Born E; Mathur S N
CORPORATE SOURCE: UNIV IOWA, DEPT INTERNAL MED, IOWA CITY, IA 52242 (Reprint); VET ADM MED CTR, IOWA CITY, IA 52242

COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF LIPID RESEARCH, (FEB 1997) Vol. 38, No. 2, pp. 348-360.
Publisher: LIPID RESEARCH INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998.
ISSN: 0022-2275.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 42

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB CaCo-2 cells were used to address the effect of the plant sterol, beta-**sitosterol**, on **cholesterol** trafficking, **cholesterol** metabolism, and apoB secretion. Compared to cells incubated with micelles (5 mM taurocholate and 250 mu M oleic acid) containing **cholesterol**, which caused an increase in the influx of plasma membrane **cholesterol** to the endoplasmic reticulum and increased the secretion of cholesteryl esters derived from the plasma membrane, beta-**sitosterol** did not alter **cholesterol** trafficking or cholesteryl ester secretion. Including beta-**sitosterol** in the micelle together with **cholesterol** attenuated the influx of plasma membrane **cholesterol** and prevented the secretion of cholesteryl esters-derived from the plasma membrane. Stigmasterol and campesterol had effects similar to beta-**sitosterol**, although campesterol did promote a modest influx of plasma membrane **cholesterol**. Including beta-**sitosterol** in the micelle with **cholesterol** decreased the uptake of **cholesterol**. Compared to **cholesterol**, 60% less beta-**sitosterol** was taken up by CaCo-2 cells. No observable esterification of beta-**sitosterol** was appreciated and the transport of the plant sterol to the basolateral medium was negligible. **Cholesterol** synthesis and **HMG-CoA** reductase activities were decreased in cells incubated with beta-**sitosterol**. This was associated with a decrease in reductase mass and mRNA levels. Cholesteryl eater synthesis and ACAT activities were unaltered by beta-**sitosterol**. Both stigmasterol and campesterol decreased reductase activity, but only campesterol increased ACAT activity. beta-**sitosterol** did not affect the secretion of apoB mass. The results suggest that beta-**sitosterol** does not promote **cholesterol** trafficking from the plasma membrane to the endoplasmic reticulum. beta-**sitosterol** interferes with the uptake of micellar **cholesterol** causing less plasma membrane **cholesterol** to influx and less cholesteryl ester to be secreted. Despite its lack of effect on **cholesterol** trafficking, beta-**sitosterol** decreases **cholesterol** synthesis at the level of **HMG-CoA**-reductase gene expression.

L27 ANSWER 16 OF 36 MEDLINE
ACCESSION NUMBER: 95221597 MEDLINE
DOCUMENT NUMBER: 95221597 PubMed ID: 7706454
TITLE: Unexpected inhibition of **cholesterol** 7 alpha-**hydroxylase** by **cholesterol** in New Zealand white and Watanabe heritable hyperlipidemic rabbits.
AUTHOR: Xu G; Salen G; Shefer S; Ness G C; Nguyen L B; Parker

T S; Chen T S; Zhao Z; Donnelly T M; Tint G S
CORPORATE SOURCE: Medical Service, Veterans Affairs Medical Center, East Orange, New Jersey 07018, USA.
CONTRACT NUMBER: DK-18707 (NIDDK)
HL-17818 (NHLBI)
HL-18094 (NHLBI)
+
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1995 Apr) 95 (4) 1497-504.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950518
Last Updated on STN: 19980206
Entered Medline: 19950509

AB We investigated the effect of **cholesterol** feeding on plasma **cholesterol** concentrations, hepatic activities and mRNA levels of **HMG-CoA** reductase and **cholesterol** 7 alpha-**hydroxylase** and hepatic LDL receptor function and mRNA levels in 23 New Zealand White (NZW) and 17 Watanabe heritable hyperlipidemic (WHHL) rabbits. Plasma **cholesterol** concentrations were 9.9 times greater in WHHL than NZW rabbits and rose significantly in both groups when **cholesterol** was fed. Baseline liver **cholesterol** levels were 50% higher but rose only 26% in WHHL as compared with 3.6-fold increase with the **cholesterol** diet in NZW rabbits. In both rabbit groups, hepatic total **HMG-CoA** reductase activity was similar and declined > 60% without changing enzyme mRNA levels after **cholesterol** was fed. In NZW rabbits, **cholesterol** feeding inhibited LDL receptor function but not mRNA levels. As expected, receptor-mediated LDL binding was reduced in WHHL rabbits. Hepatic **cholesterol** 7 alpha-**hydroxylase** activity and mRNA levels were 2.8 and 10.4 times greater in NZW than WHHL rabbits. Unexpectedly, **cholesterol** 7 alpha-**hydroxylase** activity was reduced 53% and mRNA levels were reduced 79% in NZW rabbits with 2% **cholesterol** feeding. These results demonstrate that WHHL as compared with NZW rabbits have markedly elevated plasma and higher liver **cholesterol** concentrations, less hepatic LDL receptor function, and very low hepatic **cholesterol** 7 alpha-**hydroxylase** activity and mRNA levels. Feeding **cholesterol** to NZW rabbits increased plasma and hepatic concentrations greatly, inhibited LDL receptor-mediated binding, and unexpectedly suppressed **cholesterol** 7 alpha-**hydroxylase** activity and mRNA to minimum levels similar to WHHL rabbits. Dietary **cholesterol** accumulates in the plasma of NZW rabbits, and WHHL rabbits are hypercholesterolemic because reduced LDL receptor function is combined with decreased catabolism of **cholesterol** to bile acids.

L27 ANSWER 17 OF 36 MEDLINE
ACCESSION NUMBER: 97368596 MEDLINE
DOCUMENT NUMBER: 97368596 PubMed ID: 9225210
TITLE: Effects of an **HMG-CoA** reductase

inhibitor, pravastatin, and bile sequestering resin, cholestyramine, on plasma plant sterol levels in hypercholesterolemic subjects.

AUTHOR: Hidaka H; Kojima H; Kawabata T; Nakamura T; Konaka K; Kashiwagi A; Kikkawa R; Shigeta Y

CORPORATE SOURCE: Third Department of Medicine, Shiga University of Medical Science, Japan.

SOURCE: JOURNAL OF ATHEROSCLEROSIS AND THROMBOSIS, (1995) 2 (1) 60-5.
Journal code: 9506298. ISSN: 1340-3478.

PUB. COUNTRY: Japan

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199709

ENTRY DATE: Entered STN: 19970916
Last Updated on STN: 19970916
Entered Medline: 19970902

AB To study exogenous sterol metabolism during the suppression or stimulation of **cholesterol** biosynthesis induced by treatments for hyperlipidemia, we determined plasma plant sterol concentrations before and after administration of an **HMG-CoA** reductase inhibitor, pravastatin, and compared these with changes in these plasma sterol levels by the bile-sequestrating resin, cholestyramine. The effects of the drugs were also studied in a sitosterolemic patient who has had increased plasma levels of plant sterols. Plasma **cholesterol** levels determined by the HPLC method were decreased significantly after administration of pravastatin. Plasma plant sterol (**sitosterol** and campesterol) as well as cholestanol concentrations were also significantly reduced. Cholestyramine administration decreased plasma levels of **cholesterol**, but did not change those of plant sterols in the hypercholesterolemic subjects. Pravastatin had little effect in a sitosterolemic patient on plasma levels of sterols, where cholestyramine decreased the plasma levels of both **cholesterol** and cholestanol. These results indicate that treatment with the **HMG-CoA** reductase inhibitor decreases plasma plant sterol concentrations, and suggest that the increased plasma plant sterol levels in sitosterolemia might not be due to the decreased **cholesterol** biosynthesis in vivo.

L27 ANSWER 18 OF 36 MEDLINE DUPLICATE 7

ACCESSION NUMBER: 94292111 MEDLINE

DOCUMENT NUMBER: 94292111 PubMed ID: 8020891

TITLE: The effect of increased hepatic **sitosterol** on the regulation of 3-**hydroxy**-3-**methylglutaryl-coenzyme A** -reductase and **cholesterol** 7 alpha-**hydroxylase** in the rat and sitosterolemic homozygotes.

AUTHOR: Shefer S; Salen G; Bullock J; Nguyen L B; Ness G C; Vhao Z; Belamarich P F; Chowdhary I; Lerner S; Batta A K; +

CORPORATE SOURCE: Sammy Davis Jr. National Liver Institute, University of Medicine and Newark 07103.

CONTRACT NUMBER: DK 26756 (NIDDK)
HL 17818 (NHLBI)
HL 18094 (NHLBI)

SOURCE: HEPATOLOGY, (1994 Jul) 20 (1 Pt 1) 213-9.
Journal code: 8302946. ISSN: 0270-9139.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940815
Last Updated on STN: 19940815
Entered Medline: 19940729

AB We investigated hepatic **cholesterol** homeostasis in four homozygous sitosterolemic subjects from two unrelated families who showed enhanced absorption, diminished removal and increased tissue and plasma concentrations of **sitosterol** (24-ethyl **cholesterol**). Measurements of hepatic 3-**hydroxy**-3-**methylglutaryl coenzyme A** reductase activities were correlated with steady state messenger RNA levels and related to **cholesterol** 7 alpha-**hydroxylase** activities in the sitosterolemic homozygotes and nine controls. Similar determinations were made in rats infused intravenously with **sitosterol** so that hepatic and plasma **sitosterol** concentrations increased to about 10% of total sterols to resemble the human disease sitosterolemia. In the four sitosterolemic homozygotes, hepatic 3-**hydroxy**-3-**methylglutaryl coenzyme A** reductase activities were markedly reduced (12% of normal), and steady state 3-**hydroxy**-3-**methylglutaryl coenzyme A** reductase messenger RNA levels barely detected. In contrast, hepatic 3-**hydroxy**-3-**methylglutaryl coenzyme A** reductase activities and messenger RNA levels were not decreased in rats with similarly elevated hepatic **sitosterol** concentrations. However, hepatic **cholesterol** 7 alpha-**hydroxylase** activity was inhibited 30% in both the sitosterolemic homozygotes and rats with high liver **sitosterol** concentrations. Plasma **cholesterol** concentrations increased 120% in the **sitosterol**-infused rats and 29% in the untreated human homozygotes. These results demonstrate that high-tissue **sitosterol** concentrations do not inhibit hepatic 3-**hydroxy**-3-**methylglutaryl coenzyme A** reductase activityor steady state messenger RNA levels and that they competitively block **cholesterol** 7 alpha-**hydroxylase** activity and raise plasma **cholesterol** levels. Thus the deficiency of 3-**hydroxy**-3-**methylglutaryl coenzyme A** reductase in the liver of sitosterolemic homozygotes is inherited and not due to the hepatic accumulation of **sitosterol**. (ABSTRACT TRUNCATED AT 250 WORDS)

L27 ANSWER 19 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 8

ACCESSION NUMBER: 1993:354929 BIOSIS
DOCUMENT NUMBER: PREV199345038354
TITLE: **Sitosterol** (24-ethylcholesterol) competitively inhibits **cholesterol** 7-alpha-**hydroxylase** but not **HMG-COA** reductase.
AUTHOR(S): Shefer, S. (1); Salen, G.; Bullock, J.; Nguyen, L.

B.; Ness, G. C.
CORPORATE SOURCE: (1) Dep. Med., UMD-New Jersey Med. Sch., Newark, NJ USA
SOURCE: Gastroenterology, (1993) Vol. 104, No. 4 SUPPL., pp. A991.
Meeting Info.: 94th Annual Meeting of the American Gastroenterological Association Boston, Massachusetts, USA May 15-21, 1993
ISSN: 0016-5085.
DOCUMENT TYPE: Conference
LANGUAGE: English

L27 ANSWER 20 OF 36 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 93155569 MEDLINE
DOCUMENT NUMBER: 93155569 PubMed ID: 8429265
TITLE: New model to study **cholesterol** uptake in the human intestine in vitro.
AUTHOR: Sviridov D D; Safonova I G; Nano J L; Pavlov M Y; Rampal P; Repin V S; Smirnov V N
CORPORATE SOURCE: Institute of Experimental Cardiology, Cardiology Research Center, Moscow, Russia.
SOURCE: JOURNAL OF LIPID RESEARCH, (1993 Feb) 34 (2) 331-9.
Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199303
ENTRY DATE: Entered STN: 19930326
Last Updated on STN: 19980206
Entered Medline: 19930305

AB A new model to study **cholesterol** uptake in the human intestine in vitro is described. Human small intestine organ cultures were incubated with mixed micelles containing bile acid, phospholipid, and **cholesterol** or its nonabsorbable analogue, **sitosterol**; trace amounts of labeled **cholesterol** or **sitosterol** were added to the micelles. After incubation, the lipids were extracted from the cells and **cholesterol** and **sitosterol** uptake was evaluated. Specific **cholesterol** uptake was determined as a difference between **cholesterol** and **sitosterol** uptake. **Cholesterol**, but not **sitosterol**, uptake was time- and dose-dependent. Rapid and slow phases of **cholesterol** uptake were observed. **Cholesterol** uptake was also temperature-dependent. Removal of epithelial cells from human intestine explants reduced **cholesterol**, but not **sitosterol**, uptake. Inhibition of **acyl CoA :cholesterol** acyltransferase by Sandoz compound 58-035 and treatment with monensin reduced **cholesterol** uptake, but not **sitosterol** uptake, in a dose-dependent manner. In contrast, treatment of cultures with an inhibitor of 3-**hydroxy-3-methyl-glutaryl coenzyme A** reductase, lovastatin, stimulated **cholesterol**, but not **sitosterol**, uptake in a dose-dependent manner; mevalonic acid reversed the effect of lovastatin. The presented model allows large-scale in vitro studies of different stages of **cholesterol** absorption in the human intestine.

L27 ANSWER 21 OF 36 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 93250127 MEDLINE
DOCUMENT NUMBER: 93250127 PubMed ID: 8485218
TITLE: [Regulation of **cholesterol** absorption in human and rat small intestine epithelial cells]. Reguliatsiia vsasyvaniia kholesterina v epitelial'nykh kletkakh tonkogo kishechnika cheloveka i krysy.
AUTHOR: Safonova I G; Sviridov D D; Rampal' P; Nano Zh L; Pavlov M Iu; Repin V S
CORPORATE SOURCE: Laboratory of Gastroenterology and Nutrition, Faculty of Medicine, Nice University, France.
SOURCE: BIOKHIMIIA, (1993 Feb) 58 (2) 274-84.
Journal code: 0372667. ISSN: 0320-9725.
PUB. COUNTRY: RUSSIA: Russian Federation
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930618
Last Updated on STN: 19930618
Entered Medline: 19930610

AB **Cholesterol** absorption in human small intestine organ culture and rat small intestine epithelial cell culture IRD-98 has been studied using [14C] **cholesterol**, [3H] **cholesterol** and [14C] **sitosterol**. It has been found that **cholesterol** absorption is a dose- and time-dependent process, while **sitosterol** absorption is not and makes up to about 25% of the total **cholesterol** absorption. **Cholesterol** absorption appeared to be a specific process. The endocytosis inhibitor monensin decreased specific **cholesterol** absorption by 37%. **Cholesterol** absorption was examined under different conditions influencing **cholesterol** metabolism in the cell. Loading of IRD-98 cells with non-lipoprotein **cholesterol** caused a dose-dependent decrease of **cholesterol** absorption. The inhibitor of **acyl coenzyme A:cholesterol** acyl transferase (ACAT), compound Sandoz 58-035, had a similar effect on **cholesterol** absorption. Lovastatin, an inhibitor of 3-**hydroxymethyl**-3-**glutaryl coenzyme A** (**HMG-CoA**) reductase, stimulated **cholesterol** absorption in a dose-dependent manner. Loading of cells with **cholesterol**, lovastatin and Sandoz 58-035 had no effect on **sitosterol** absorption. The possibility has been demonstrated of using human small intestine organ culture and rat small intestine epithelial cell culture IRD-98 as models for studying **cholesterol** absorption.

L27 ANSWER 22 OF 36 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 93:566709 SCISEARCH
THE GENUINE ARTICLE: LX403
TITLE: REGULATION OF ABSORPTION OF **CHOLESTEROL** IN EPITHELIAL-CELLS OF HUMAN AND RAT SMALL-INTESTINE
AUTHOR: SAFONOVA I G (Reprint); SVIRIDOV D D; RAMPAL P; NANO J L; PAVLOV M Y; REPIN V S
CORPORATE SOURCE: RUSSIAN ACAD MED SCI, CARDIOL RES CTR, INST EXPTL

CARDIOL, MOSCOW, RUSSIA (Reprint); UNIV NICE, SCH MED, GASTROENTEROL & NUTR LAB, F-06034 NICE, FRANCE
COUNTRY OF AUTHOR: RUSSIA; FRANCE
SOURCE: BIOCHEMISTRY-RUSSIA, (FEB 1993) Vol. 58, No. 2, pp. 154-161.
ISSN: 0006-2979.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 36

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Cholesterol** absorption in human small intestine organ culture and rat small intestine epithelial cell culture IRD-98 was studied using [C-14]**cholesterol**, [H-3]**cholesterol**, and [C-14]**sitosterol**. Absorption of **cholesterol** was shown to be a dose- and time-dependent specific process. **Sitosterol** absorption was concentration-independent, showed no time trend, and accounted for approximately 25% of the total absorption of **cholesterol**. Monensin, an inhibitor of endocytosis, reduced the specific absorption of **cholesterol** by 37%. Absorption of **cholesterol** was studied under different conditions affecting its cellular metabolism. Loading the IRD-98 cells with lipoprotein-free **cholesterol** resulted in a dose-dependent decrease in **cholesterol** absorption. A similar effect was produced by administration of compound 58-035 (Sandoz), an inhibitor of **acyl-CoA**: **cholesterol** acyl transferase. Lovastatin, an inhibitor of 3-**hydroxymethyl**-3-**glutaryl-CoA** reductase, caused dose-dependent activation of **cholesterol** absorption. Loading the cells with **cholesterol** and administration of lovastatin or Sandoz 58-035 did not affect the absorption of **sitosterol**. Human small intestine organ culture and the culture of rat small intestine IRD-98 cells proved useful as models to study the absorption of **cholesterol**.

L27 ANSWER 23 OF 36 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 93085854 MEDLINE
DOCUMENT NUMBER: 93085854 PubMed ID: 1453550
TITLE: Effects of pravastatin on **cholesterol** metabolism in Watanabe heritable hyperlipidemic rabbits.
AUTHOR: Amorosa L F; Rozovski S J; Ananthakrishnan R; Coly E; AlHinai A; Martucci C; Schneider S H; Shimamura T; Khachadurian A K
CORPORATE SOURCE: UMDNJ-Robert Wood Johnson Medical School, Department of Medicine, New Brunswick, New Jersey 08903-0019.
SOURCE: JAPANESE HEART JOURNAL, (1992 Jul) 33 (4) 451-63.
Journal code: 0401175. ISSN: 0021-4868.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199301
ENTRY DATE: Entered STN: 19930129
Last Updated on STN: 19980206
Entered Medline: 19930104

AB Pravastatin, a competitive inhibitor of **hydroxymethylglutaryl CoA** reductase (**HMG**

CoA reductase) is a potent hypocholesterolemic agent in humans as well as experimental animals, including the Watanabe heritable hyperlipidemic (WHHL) rabbit, lacking low density lipoprotein (LDL) receptor activity. We studied the effect of pravastatin on several aspects of **cholesterol** metabolism in WHHL rabbits. **Cholesterol** synthesis was measured by intraperitoneal injection of radioacetate and determination of its incorporation into the nonsaponifiable lipid fraction of liver, plasma, adrenal glands and gonads. A single dose of pravastatin (25 mg/kg) caused statistically significant inhibition of hepatic **cholesterol** synthesis at 2, 6, 12, and 24 hours following oral administration. By 48 hours, the inhibitory effect of the drug was no longer demonstrable. The pattern of radioactivity in the plasma was similar to that in the liver. The drug had no statistically significant effect on **cholesterol** synthesis in adrenal glands and gonads, suggesting a selective effect on the liver. **Cholesterol** absorption was studied after simultaneous oral administration of [3H] **cholesterol** and [14C] beta-**sitosterol**. Pravastatin, 50 mg/kg for 10 days had no effect on fecal excretion of the radiolabelled steroids over 4 days. At 24 hours the plasma level of [14C] **cholesterol** was 1/3 that of control in pravastatin treated animals ($p < 0.05$) but did not undergo an accelerated decline over 6 days. The activity of **acyl CoA: cholesterol** acyltransferase (ACAT) in intestinal mucosa and the concentration of hepatic **cholesterol** were similar in animals treated over one year with pravastatin 50 mg/kg/day or with placebo. Our data do not allow us to make definitive conclusions about the effect of pravastatin on **cholesterol** absorption but are compatible with the hypothesis that the drug inhibits the hepatic synthesis as well as the assembly of **cholesterol** into lipoproteins.

L27 ANSWER 24 OF 36 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 91:259389 SCISEARCH
THE GENUINE ARTICLE: FJ004
TITLE: INHIBITION OF **CHOLESTEROL** ABSORPTION AND SYNTHESIS IN RATS BY SESAMIN
AUTHOR: HIROSE N; INOUE T; NISHIHARA K; SUGANO M (Reprint); AKIMOTO K; SHIMIZU S; YAMADA H
CORPORATE SOURCE: KYUSHU UNIV, SCH AGR 4609, NUTR CHEM LAB, HIGASHI KU, FUKUOKA 812, JAPAN; KYUSHU UNIV, FAC MED, DEPT PATHOL 2, FUKUOKA 812, JAPAN; KYOTO UNIV, DEPT AGR CHEM, KYOTO 606, JAPAN; SUNTORY LTD, INST FUNDAMENTAL RES, OSAKA 618, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: JOURNAL OF LIPID RESEARCH, (1991) Vol. 32, No. 4, pp. 629-638.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 34
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The effects of sesamin, a lignan from sesame oil, on various aspects of **cholesterol** metabolism were examined in rats maintained on various dietary regimens. When given at a dietary level of 0.5% for 4 weeks, sesamin reduced the concentration of serum and liver **cholesterol** significantly irrespective of the presence or absence of **cholesterol** in the diet, except

for one experiment in which the purified diet free of **cholesterol** was given. On feeding sesamin, there was a decrease in lymphatic absorption of **cholesterol** accompanying an increase in fecal excretion of neutral, but not acidic, steroids, particularly when the **cholesterol** -enriched diet was given. Sesamin inhibited micellar solubility of **cholesterol**, but not bile acids, whereas it neither bound taurocholate nor affected the absorption of fatty acids. Only a marginal proportion (ca. 0.15%) of sesamin administered intragastrically was recovered in the lymph. There was a significant reduction in the activity of liver microsomal 3-**hydroxy**-3-**methylglutaryl coenzyme** **A** reductase after feeding sesamin, although the activity of hepatic **cholesterol** 7-alpha-**hydroxylase**, drug metabolizing enzymes, and alcohol dehydrogenase remained uninfluenced. Although the weight and phospholipid concentration of the liver increased unequivocally on feeding sesamin, the histological examination by microscopy showed no abnormality, and the activity of serum GOT and GPT remained unchanged.

Since sesamin lowered both serum and liver **cholesterol** levels by inhibiting absorption and synthesis of **cholesterol** simultaneously, it deserves further study as a possible hypocholesterolemic agent of natural origin.

L27 ANSWER 25 OF 36 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 89313130 MEDLINE
DOCUMENT NUMBER: 89313130 PubMed ID: 2747429
TITLE: Effect of dietary n-3 polyunsaturated fatty acids on **cholesterol** synthesis and degradation in rats of different ages.
AUTHOR: Choi Y S; Goto S; Ikeda I; Sugano M
CORPORATE SOURCE: Laboratory of Nutrition Chemistry, School of Agriculture, Kyushu University, Fukuoka, Japan.
SOURCE: LIPIDS, (1989 Jan) 24 (1) 45-50.
Journal code: 0060450. ISSN: 0024-4201.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198908
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19970203
Entered Medline: 19890825

AB Male Sprague-Dawley rats four weeks or eight months of age were fed purified diets containing 10% fat, either as a blend of safflower oil and palm olein (polyunsaturated fatty acids, PUFA, 34%), a blend of linseed oil and palm olein (PUFA, 33%) or sardine oil (PUFA, 33%) for four weeks. In other trials, sterol contents were made equivalent by supplementing **cholesterol** to a blend of corn oil and palm olein (PUFA, 30%) or **phytosterol** to sardine oil (PUFA, 30%). Fish oil was hypolipidemic in rats of different ages, but it tended to increase liver **cholesterol** in adult animals and this was not improved by the addition of **phytosterol**. The age-dependent increase in liver **cholesterol** was not duplicated in rats fed a vegetable fat blend supplemented with **cholesterol**. At both ages, liver 3-**hydroxy**-3-**methylglutaryl coenzyme** **A** reductase activity was lower in the sardine oil than in

the other groups. There were no significant age- or diet-related differences in the activity of liver **cholesterol** 7 alpha-**hydroxylase**. Fecal steroid excretion was comparable in age-matched rats fed diets supplemented either with **cholesterol** or **phytosterol**. Sardine oil reduced the delta 6-desaturase activity markedly as compared with linseed oil, and age-dependent reduction of the desaturase activity was observed in all dietary groups examined. Thus, the results showed a specific effect of fish oil on lipid metabolism.

L27 ANSWER 26 OF 36 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 89313140 MEDLINE
DOCUMENT NUMBER: 89313140 PubMed ID: 2747437
TITLE: Effect of **sitosterol** on the rate-limiting enzymes in **cholesterol** synthesis and degradation.
AUTHOR: Boberg K M; Akerlund J E; Bjorkhem I
CORPORATE SOURCE: Institute of Clinical Biochemistry, University of Oslo, Norway.
SOURCE: LIPIDS, (1989 Jan) 24 (1) 9-12.
Journal code: 0060450. ISSN: 0024-4201.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198908
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19970203
Entered Medline: 19890825

AB Attempts were made to develop an animal model for phytosterolemia. Infusion of Intralipid containing 0.2% **sitosterol** in rats gave circulating levels of **sitosterol** of about 2.5 mmol/l, which is similar to or higher than those present in patients with untreated phytosterolemia. In addition, the infusions gave serum levels of **cholesterol** nearly twice those obtained in rats infused with Intralipid alone or Intralipid containing 0.2% **cholesterol**. The hepatic **HMG-CoA** reductase activity was unaffected or slightly increased by the **sitosterol** infusions (not statistically significant). The **cholesterol** 7 alpha-**hydroxylase** activity was slightly depressed (ca. 30%). In the case of 7 alpha-hydroxylation of endogenous **cholesterol**, the depression reached statistical significance (p less than 0.05). The microsomal content of **sitosterol** in the **sitosterol**-infused rats was about 30% of that of microsomal **cholesterol**. The effect of **sitosterol** on 7 alpha-hydroxylation of **cholesterol** was investigated by incubations of acetone powder of rat liver microsomes with mixtures of **cholesterol** and **sitosterol**. **Sitosterol** mixed with **cholesterol** to a composition similar to that found in the above microsomal fraction had a depressing effect on 7 alpha-hydroxylation of **cholesterol**. This degree of depression was of the same magnitude as that found in the **sitosterol** infusion experiments. The possibility is discussed that the hypercholesterolemia obtained in the beta-**sitosterol**-infused rats is due to the inhibitory effect of **sitosterol** on the **cholesterol** 7 alpha-**hydroxylase**.

L27 ANSWER 27 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 88100987 EMBASE
DOCUMENT NUMBER: 1988100987
TITLE: Mode of action of lipid-lowering drugs.
AUTHOR: Fears R.
CORPORATE SOURCE: Beecham Pharmaceuticals Research Division, Epsom KT18 5XQ, United Kingdom
SOURCE: Bailliere's Clinical Endocrinology and Metabolism, (1987) 1/3 (727-754).
ISSN: 0950-351X CODEN: BCEMEJ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 003 Endocrinology
037 Drug Literature Index
038 Adverse Reactions Titles
029 Clinical Biochemistry
018 Cardiovascular Diseases and Cardiovascular Surgery
006 Internal Medicine
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Following the recent demonstration that both cholestyramine and nicotinic acid decrease mortality from coronary heart disease, there is a new enthusiasm for hypolipaemic therapy. The agents in current use are, however, insufficiently active or are accompanied by unacceptable side effects. An understanding of the mode of action is necessary, both to optimize treatment guidelines (e.g. regarding combination therapy or use in specific subsets of patients) and to develop new agents with preferred actions on rate-limiting steps. A reduction in LDL **cholesterol** concentration remains the principal desired action, although an elevation in HDL may also be beneficial. The main categories of commercially available agent comprise the anion exchange resins (inhibitors of bile acid absorption); **cholesterol** absorption inhibitors; fibrates (probably acting by enhancing lipoprotein lipase); and probucol (affecting LDL clearance). The most interesting of the new agents in clinical trials are the .beta.-**hydroxy**-.beta.-**methylglutaryl-CoA** reductase inhibitors, but other types of agent are at an earlier stage of evaluation, e.g. **acyl-CoA:cholesterol** acyltransferase inhibitors and peptide cofactors. It is not yet certain whether all the approaches to **cholesterol** lowering have equal validity, although an effect on biological endpoints is obtained for a variety of agents. Future evaluation will be aided by the implementation of noninvasive methods to quantify atherosclerosis and by the use of simple, 'dry-chemistry', **cholesterol** assays to screen populations.

L27 ANSWER 28 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 85014091 EMBASE
DOCUMENT NUMBER: 1985014091
TITLE: Comparative effects of cholestanol and **cholesterol** on hepatic sterol and bile acid metabolism in the rat.
AUTHOR: Shefer S.; Hauser S.; Salen G.; et al.
CORPORATE SOURCE: Department of Medicine, University of Medicine and Dentistry of New Jersey, New Jersey Medical School,

Newark, NJ 07103, United States
SOURCE: Journal of Clinical Investigation, (1984) 74/5 (1773-1781).
CODEN: JCINAO
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
048 Gastroenterology
023 Nuclear Medicine
029 Clinical Biochemistry
LANGUAGE: English

AB Large amounts of cholestanol, the 5.alpha.-dihydro derivative of **cholesterol** are found in tissues of patients with the rare inherited sterol storage disease cerebrotendinous xanthomatosis. Although small amounts of cholestanol are present in virtually every tissue of normal man, little is known about its metabolism and effect on **cholesterol** and bile acid formation. The purpose of this study is to investigate the absorption and metabolism of cholestanol and its early effects on hepatic morphology and on the rate-limiting enzymes of **cholesterol** and bile acid biosynthesis. After 2 wk on a diet supplemented with 2% cholestanol, total liver sterol content increased by 48% (3.26 vs. 2.20 mg/g), and resulted in a significant rise in hepatic cholestanol concentration to 1.4 mg/g. However, cholestanol was less efficiently absorbed from the intestine than **cholesterol** and interfered with **cholesterol** absorption. Furthermore, hepatic **hydroxymethylglutaryl-coenzyme A** (**HMG-CoA**) reductase activity rose 2.6-fold (from 150.3 to 397.0 pmol/mg per min) during cholestanol feeding, and was associated with a marked proliferation of the smooth endoplasmic reticulum of the centrilobular areas. In addition, significant amounts of allocholic acid (16%) and allochenodeoxycholic acid (5%) were formed from cholestanol and excreted in the bile. These results show that **cholesterol** is absorbed from the intestine, interferes with **cholesterol** absorption, and is deposited in the liver. However, in contrast to **cholesterol**, cholestanol feeding was associated with a marked elevation of **HMG-CoA** reductase activity. Thus, despite structural similarity between **cholesterol** and its 5.alpha.-saturated derivative, cholestanol does not exert feedback inhibition on hepatic **cholesterol** biosynthesis.

L27 ANSWER 29 OF 36 MEDLINE DUPLICATE 14

ACCESSION NUMBER: 84266547 MEDLINE
DOCUMENT NUMBER: 84266547 PubMed ID: 6547738
TITLE: Role of hydrophilic bile acids and of sterols on cholelithiasis in the hamster.
AUTHOR: Singhal A K; Cohen B I; Finver-Sadowsky J; McSherry C K; Mosbach E H
CONTRACT NUMBER: HL-24061 (NHLBI)
SOURCE: JOURNAL OF LIPID RESEARCH, (1984 Jun) 25 (6) 564-70.
Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198409
ENTRY DATE: Entered STN: 19900320

Last Updated on STN: 19970203
Entered Medline: 19840906

AB The effect of various dietary additions such as **cholesterol**, beta-**sitosterol**, bile acids, and bile acid analogs on gallstone formation was studied in the hamster. Gallstones were formed in 50% of the animals fed a high glucose, fat-free diet. Administration of 0.2% **cholesterol** or 1% beta-**sitosterol** had no effect on the incidence of gallstones. Ursodeoxycholic acid (0.5%) and its analog ursodeoxy-oxazoline [2-(3 alpha, 7 beta-dihydroxy-24-nor-5 beta-cholanyl)-4,4-dimethyl-2-oxazoline] were ineffective in preventing gallstones. Hyodeoxycholic acid and hyodeoxy-oxazoline [2-(3 alpha,6 alpha-dihydroxy-24-nor-5 beta-cholanyl)-4,4-dimethyl-2- oxazoline] at the same dosage effectively prevented gallstones, while the trihydroxy bile acid, hyocholic acid, was not effective. Of all the dietary regimens tested, only hyodeoxycholic acid significantly lowered serum **cholesterol**. The lithogenic diet produced a five-fold increase in hepatic **HMG-CoA** reductase activity; this activity was not affected by dietary **cholesterol** or beta-**sitosterol**. Hyodeoxycholic acid and hyocholic acid feeding increased the reductase activity by an additional 50% while the other bile acids had no effect. beta-**Sitosterol** doubled the **cholesterol** 7 alpha-**hydroxylase** activity whereas hyodeoxy-oxazoline lowered it. Hyodeoxycholic acid-fed animals had significantly lower **cholesterol** absorption than the animals on the lithogenic diet alone. Biliary **cholesterol** content increased dramatically in the animals fed the lithogenic diet and was increased still further by ursodeoxycholic acid, hyodeoxycholic acid, and hyodeoxy-oxazoline. These data show that hyodeoxycholic acid and hyodeoxy-oxazoline do not prevent gallstones by inhibiting hepatic **cholesterol** synthesis or biliary **cholesterol** secretion.

L27 ANSWER 30 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 83118221 EMBASE
DOCUMENT NUMBER: 1983118221
TITLE: Early morphologic and enzymatic changes in livers of rats treated with chenodeoxycholic and ursodeoxycholic acids.
AUTHOR: Shefer S.; Zaki F.G.; Salen G.
CORPORATE SOURCE: Dep. Med., Univ. Med. Dent. New Jersey/New Jersey Med. Sch., Newark, NJ 07103, United States
SOURCE: Hepatology, (1983) 3/2 (201-208).
CODEN: HPTLD
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
048 Gastroenterology
005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
LANGUAGE: English

AB The effect of high doses of chenodeoxycholic and ursodeoxycholic acids on hepatic morphology and on **cholesterol** and bile acid metabolism was examined in the rat. After 2 weeks of either cheno- or ursodeoxycholic acid feeding, the livers of the treated rats revealed marked proliferation of the smooth endoplasmic reticulum which appeared as an adaptation phenomenon of the microsomal enzyme system in response to bile acid intake. However,

the livers of the chenodeoxycholic acid-treated rats showed early alteration that included mild triaditis, swelling of the bile canalicular microvilli, distended Golgi vesicles, whorling of the mitochondria, and presence of large vacuoles bound by single membranes. During cheno- or ursodeoxycholic acid treatment, the administered bile acid predominated in the bile and amounted to 79 or 67% of the biliary bile acids, respectively. At the same time, the concentration of the muricholic acids was also increased. Biliary cholic acid content dropped significantly, but no change in lithocholic acid concentration was observed. In addition, the activity of **HMG-CoA** reductase as well as that of **cholesterol**-7.alpha.-**hydroxylase** was reduced by either of the administered bile acids, while no change in hepatic **cholesterol** content was detected, and intestinal **cholesterol** absorption was not significantly different from that of controls. These results show that cheno- and ursodeoxycholic acids inhibited hepatic **cholesterol** and bile acid synthesis but did not increase either intestinal **cholesterol** absorption or hepatic microsomal **cholesterol** content. Since the amounts of biliary lithocholic acid were similar in the bile acid-treated animals, the morphologic abnormalities detected in the chenodeoxycholic acid-fed rats are probably due to an increased pool of chenodeoxycholic acid. However, lithocholic acid-induced liver injury cannot be excluded.

L27 ANSWER 31 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 82130856 EMBASE
DOCUMENT NUMBER: 1982130856
TITLE: Hepatic **cholesterol** absorption in patients with gallstones. Effect of cicloxilic acid: A preliminary report.
AUTHOR: Carulli N.; Ponz de Leon M.; Iori R.; et al.
CORPORATE SOURCE: Ist. Clin. Med. II, Univ. Modena, Italy
SOURCE: Italian Journal of Gastroenterology, (1981) 13/4 (239-343).
CODEN: ITJGDH
COUNTRY: Italy
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
048 Gastroenterology
003 Endocrinology
006 Internal Medicine
029 Clinical Biochemistry
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: Italian
AB It has been shown that cicloxillic acid, a hydrocholeretic agent, may lower bile **cholesterol** saturation. To further elucidate the responsible mechanism, the effect of cicloxilic acid on **cholesterol** absorption and hepatic sterol metabolism was investigated in 10 gallstone patients. The compound was given orally for 2-3 weeks at a dose of 240 mg/day. In 5 subjects, **cholesterol** absorption was evaluated before and at the end of the treatment, each patient acting as his own control. In the remaining 5 subjects surgical liver biopsies were obtained during cholecystectomy, performed at the end of treatment. **HMG-CoA** reductase, 7.alpha.-**hydroxylase** activities and microsomal **cholesterol** were estimated in the liver

specimen. Bile lipid and bile acid composition were estimated in all patients before and after treatment. Mean basal saturation index (1.41 .+-. 0.23) fell significantly (P<0.01) to 1.17 .+-. 0.11 after treatment. Biliary bile acid composition was unaffected by treatment. Mean **cholesterol** absorption after treatment did not differ from the basal value. Similarly, the values of **HMG-CoA** reductase (64.5 .+-. 22.3 p. mol/min. mg protein), 7.alpha.-**hydroxylase** (29.5 .+-. 4.3 p. mol/min/mg protein) and microsomal **cholesterol** (69.2 .+-. 13.5 ng/mg protein) observed after treatment were comparable to those found in untreated controls. It is suggested that the efficacy of cicloxilic acid in lowering biliary **cholesterol** saturation is not mediated by changes in the absorption or hepatic synthesis of **cholesterol**.

L27 ANSWER 32 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 80202000 EMBASE
DOCUMENT NUMBER: 1980202000
TITLE: Effect of neonatal modulation of **cholesterol** homeostasis on subsequent response to **cholesterol** challenge in adult guinea pig.
AUTHOR: Li J.R.; Bale L.K.; Kottke B.A.
CORPORATE SOURCE: Cardiovasc. Res. Unit, Mayo Clin. Found., Rochester, Minn. 55901, United States
SOURCE: Journal of Clinical Investigation, (1980) 65/5 (1060-1068).
CODEN: JCINAO
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
029 Clinical Biochemistry
LANGUAGE: English

AB Experiments were designed to study whether or not the mechanism of handling dietary **cholesterol** in adulthood can be modulated by the manipulation of **cholesterol** homeostasis during neonatal period. The effects of enhancing **cholesterol** degradation (cholestyramine feeding), high dietary **cholesterol** intake, and early weaning during neonatal period of guinea pigs on their subsequent plasma **cholesterol** levels and the response to dietary **cholesterol** challenged in adulthood were investigated. Pretreatment of neonatal guinea pigs with cholestyramine resulted in (a) a lower plasma **cholesterol** level, (b) an increased excretion rate of fecal bile acids and total steroids, (c) an expanded bile acid pool, (d) an increased activity of **cholesterol** 7.alpha.-**hydroxylase**, and (e) no change in the hepatic 3-hydroxy-3-methylglutarly coenzyme A (CoA) reductase activity when challenged with **cholesterol** in adulthood. **Cholesterol** pretreatment during neonatal period resulted in (a) no alteration in the plasma **cholesterol** level, (b) no alteration in the fecal excretion of steroids, or (c) no alteration in the **cholesterol** 7.alpha.-**hydroxylase** activity when they were challenged with a high **cholesterol** diet. Early weaning did not influence the fecal excretion of steroids or **cholesterol** 7.alpha.-**hydroxylase** activity but resulted in a slight decrease in the hepatic 3-**hydroxy**-3-**methylglutaryl-CoA** reductase activity when they were challenged with a high **cholesterol** diet. These

results suggest that stimulation of **cholesterol** catabolism rather than **cholesterol** feeding or early weaning during neonatal period can influence the response to dietary **cholesterol** challenge in adulthood.

L27 ANSWER 33 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 78122812 EMBASE
DOCUMENT NUMBER: 1978122812
TITLE: Effects of cholestyramine on **cholesterol** balance parameters and hepatic **HMG CoA** reductase and **cholesterol** 7 .alpha. **hydroxylase** activities in swine.
AUTHOR: Kim D.N.; Rogers D.H.; Li J.R.; et al.
CORPORATE SOURCE: Dept. Pathol., Neill Hellman Med. Res. Bldg, Albany Med. Coll., Albany, N.Y. 12208, United States
SOURCE: Experimental and Molecular Pathology, (1977) 26/3 (434-447).
CODEN: EXMPA6
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
LANGUAGE: English
AB Effects of cholestyramine treatment for 75 days on whole body **cholesterol** balance and hepatic **HMG CoA** reductase and **cholesterol** 7 .alpha. **hydroxylase** activities were studied in hypercholesterolemic swine. Sixteen male Yorkshire swine (10 kg) were divided into 4 groups; 3 groups were fed a high **cholesterol** (HC) diet for 50 days. One group was then switched to mash, the second was given cholestyramine, 12 g daily, and the third was left on the high **cholesterol** diet, all for an additional 75 days. The fourth group was maintained on mash throughout the 125 days. Data for the **cholesterol** balance parameters, retention, excretion, and synthesis, were obtained during the terminal week. Hepatic **HMG CoA** reductase and **cholesterol** 7 .alpha. **hydroxylase** activities were assayed terminally. Cholestyramine reduced serum **cholesterol** concentrations in hypercholesterolemic swine very effectively although the reduction was not as complete as in those swine switched to mash diet. The drug also reduced whole body **cholesterol** retention. These changes appeared to be due to increases in both acidic and neutral steroids in the feces. Accompanying increases in whole body **cholesterol** synthesis probably partially offset the beneficial effect of increased steroid excretions. In vitro hepatic **HMG CoA** reductase activities correlated well with whole body **cholesterol** synthesis determined by the balance method as well as with fecal steroid excretions. **Cholesterol** 7 .alpha. **hydroxylase** activities of the liver microsomes correlated well with the amount of fecal bile acid excretion.

L27 ANSWER 34 OF 36 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 75164915 MEDLINE
DOCUMENT NUMBER: 75164915 PubMed ID: 1137717
TITLE: Sterol balance studies in the rat. Effects of dietary **cholesterol** and beta-**sitosterol** on sterol balance and rate-limiting enzymes of sterol

metabolism.
AUTHOR: Raicht R F; Cohen B I; Shefer S; Mosbach E H
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (1975 Jun 23) 388 (3) 374-84.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197509
ENTRY DATE: Entered STN: 19900310
Last Updated on STN: 19970203
Entered Medline: 19750909

AB Sterol balance measurements using isotopic and chromatographic techniques were carried out in rats fed diets containing beta-**sitosterol** (0.8%) and **cholesterol** (1.2%). The activities of the rate-limiting enzymes of **cholesterol** synthesis (beta-**hydroxy**-beta-**methylglutaryl**-**CoA** reductase, EC 1.1.1.34) and bile acid synthesis (**cholesterol** 7 alpha-**hydroxylase**) were determined in the same animals. **Cholesterol** feeding increased **cholesterol** absorption from 1.2 to 70 mg/day. The increased absorption was compensated for by inhibition of hepatic **cholesterol** synthesis, enhanced conversion of **cholesterol** to bile acids (from 13.7 to 27.3 mg/day) and a slight increase in the excretion of endogenous neutral steroids (from 7.7 to 11.2 mg/day). Despite the adaptation there was accumulation of **cholesterol** in the liver (from 2.2 to 9.2 mg/g). Beta-**Sitosterol** feeding inhibited **cholesterol** absorption (calculated absorption was zero). In these rats there was enhanced **cholesterol** synthesis (from 20.0 to 28.8 mg/day, but no change in the rates of bile acid formation. Measurements of the activities of the rate-limiting enzymes showed fair correlation with **cholesterol**-bile acid balance. In **cholesterol** fed animals, beta-**hydroxy** -beta-**methylglutaryl**-**CoA** reductase was inhibited 80% and **cholesterol** 7 alpha-**hydroxylase** was enhanced 61%. In beta-**sitosterol**-fed animals, the reductase was increased 2-fold and **cholesterol** 7 alpha-**hydroxylase** was not significantly different from controls.

L27 ANSWER 35 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1974:37639 BIOSIS
DOCUMENT NUMBER: BR10:37639
TITLE: RATE CONTROL OF STEROL METABOLISM IN RATS EFFECTS OF STEROLS OF STEROLS AND BILE ACIDS.
AUTHOR(S): RAICHT R F; COHEN B I; SHEFER S; MOSBACH E H
SOURCE: Fed. Proc., (1974) 33 (3 PART 1), 689.
CODEN: FEPRA7. ISSN: 0014-9446.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: Unavailable

L27 ANSWER 36 OF 36 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 73250408 MEDLINE
DOCUMENT NUMBER: 73250408 PubMed ID: 4729973
TITLE: Regulatory effects of sterols and bile acids on hepatic 3-**hydroxy**-3-**methylglutaryl**

	CoA reductase and **cholesterol** 7alpha-**hydroxylase** in the rat.
AUTHOR:	Shefer S; Hauser S; Lapar V; Mosbach E H
SOURCE:	JOURNAL OF LIPID RESEARCH, (1973 Sep) 14 (5) 573-80. Journal code: 0376606. ISSN: 0022-2275.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	197311
ENTRY DATE:	Entered STN: 19900310 Last Updated on STN: 19900310 Entered Medline: 19731109

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